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Arthritis Care & Research

Aims and Scope

Arthritis Care & Research is an official journal of the American College of Rheumatology and the Association of Rheumatology Professionals, a division of the College. *Arthritis Care & Research* is a peer-reviewed journal that publishes both original research and review articles that promote excellence in the clinical practice of rheumatology. Relevant to the care of individuals with arthritis and related disorders, major topics are evidence-based practice studies, clinical problems, practice guide-lines, health care economics, health care policy, educational, social, and public health issues, and future trends in rheumatology practice.

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Cover image: The image on the cover (from Gaine et al, page 1708) shows Gottron's papules on the dorsum of the metacarpophalangeal and interphalangeal joints of a patient's hands.

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American College of Rheumatology
Empowering Rheumatology Professionals

CLINICOPATHOLOGIC CONFERENCE

A 70-Year-Old Male With Hypertensive Emergency

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CASE PRESENTATION

Chief symptoms

A 70-year-old Caucasian male patient was referred to the rheumatology clinic for abnormal findings on computed tomography (CT) imaging of the abdomen and pelvis demonstrating thickening of large- and medium-sized arterial vessels associated with a high erythrocyte sedimentation rate (ESR).

History of present illness

Four months prior to presentation to the rheumatology office, the patient was admitted to the hospital with severe, persistent dental pain around the mandibular right third molar for which he had a tooth extraction. The pain continued despite the procedure. Three days later, the patient was readmitted with 20 minutes of vision loss in the left eye and 3 days of constant occipital headache radiating to the posterior neck. He was febrile with a temperature of 101°F, blood pressure reading of 154/80 mm Hg, pulse rate of 90 beats per minute, and oxygen saturation of 94% on room air. There was a concern for meningitis due to the presence of fever and occipital headache. Endocarditis was suspected due to the recent dental surgery. However, CT images of the head and neck, magnetic resonance imaging (MRI) of the brain, and CT images of the maxillofacial area with contrast were unrevealing. Evaluation for infectious disease including blood cultures and a transthoracic echocardiogram did not suggest infection. The lumbar puncture performed prior to antibiotic administration showed a normal cell count and glucose level, but a mildly elevated level of protein at 47.4 mg/dl (reference 15–45 mg/dl). Nonetheless, while awaiting Gram stain and culture, the patient was broadly treated with vancomycin, ceftriaxone, and ampicillin. Intravenous dexamethasone at a dosage of 10 mg every 6 hours for 2 days was also given as part of the empirical treatment due to suspicion of bacterial meningitis. The patient was discharged from the hospital in stable condition with improvement of headache and neck pain.

One month prior, the patient was hospitalized for hypertensive emergency complicated by pulmonary edema and hypoxic respiratory failure. His blood pressure reading at the time was 193/100 mm Hg. His presentation was thought to be due to exacerbation of chronic obstructive pulmonary disease (COPD). Therefore, he received antihypertensive medication, intravenous diuretic, intravenous albuterol, and ipratropium nebulizer treatments. As part of the treatment for COPD exacerbation, the patient also received 60 milligrams of intravenous solumedrol twice daily. No further imaging was performed as the patient's blood pressure and respiratory symptoms improved on the fifth day of hospitalization. He was discharged in stable condition.

Two weeks after discharge, the patient presented to his primary care physician with recurrence of symptoms of occipital headache and mandibular toothache. Despite receiving antihypertensive medications, he remained hypertensive with a blood pressure reading of 180/100 mm Hg. He denied any pulmonary complaints. A renal ultrasound with Doppler was initially ordered to exclude renal artery stenosis as a cause of his uncontrolled hypertension, but the renal arteries were not visualized due to extensive bowel gas. A CT of the abdomen and pelvis with contrast was subsequently performed. Imaging showed concentric wall thickening of the visualized descending thoracic aorta, splenic artery, portions of the abdominal aorta, the common iliac arteries, and renal artery branches to the right kidney along with ischemic changes of the right renal parenchyma (Figures 1 and 2). Based on the extent of the vasculature involved, systemic vasculitis was suspected. After discussion with the rheumatology department, additional laboratory data were ordered (Table 1), and the patient was initiated on a regimen of 60 mg of prednisone daily by his primary care physician.

During the rheumatology office visit, the patient reported overall improvement since prednisone initiation 2 weeks ago. When asked about his previous major complaint, he revealed that

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No potential conflicts of interest relevant to this article were reported.

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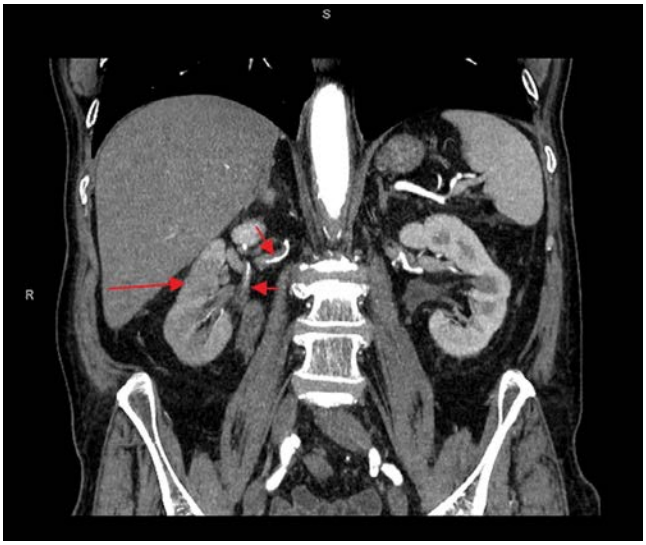

Figure 1. Computed tomography of the patient's abdomen at diagnosis, showing thickening of the walls of right renal artery branches (**short arrows**) and ischemia of right renal parenchyma (**long arrow**).

it was his severe toothache that brought him to the hospital initially, which had persisted intermittently over the past 5 months.

Medical, social, and family history

The patient's past medical history was notable for positive results on a purified protein derivative (PPD) skin test (indicated infection went untreated), COPD, gastroesophageal reflux disease, hypothyroidism, coronary artery disease, daily alcohol abuse, dermatitis, depression, hypertension, and left inguinal hernia. His medications included albuterol inhaler, budesonide/formoterol inhaler, tiotropium bromide inhaler, 81 mg of aspirin once daily, 25 mg of carvedilol twice daily, 60 mg of extended-release nifedipine once daily, 0.125 mg of levothyroxine in the morning, 20 mg of simvastatin daily, 600 mg of gabapentin twice daily, and 60 mg of prednisone that had been started 2 weeks prior to his visit to our clinic. The patient was unemployed and lived alone. He had a 15-pack per year smoking history and had quit smoking a few years prior to his visit to the rheumatology clinic. He admitted to consuming 6–10 beers daily. The patient denied any past or recent use of illicit drugs and denied any family history of autoimmune disease or malignancy.

Review of systems

The patient denied shoulder or hip girdle pain, arthralgias, myalgias, fever, chills, night sweats, photophobia, photosensitivity, skin rash, mucosal ulcers, xerostomia, keratoconjunctivitis sicca, alopecia, ear pain or swelling, sinus disease, Raynaud's phenomenon, chest pain, postprandial or any abdominal pain, hematuria, melena, or hematochezia. He denied further visual loss, headache, or dental pain.

Physical examination

On examination, the patient was in no acute distress. He had a temperature of 98.5°F, blood pressure reading of 149/72 mm Hg, and pulse rate of 75 beats per minute. His oxygen saturation was 98% while he was breathing ambient air. There was no temporal tenderness, but temporal pulse was weaker on the left than the right. He did not have any restriction on range of motion of the cervical spine. His nasal and oral mucosa was normal. There was no audible bruit over the carotid or subclavian arteries. There was no tenderness over the sinuses and no ear swelling or redness. Superficial lymph nodes were not palpable. Breath sounds

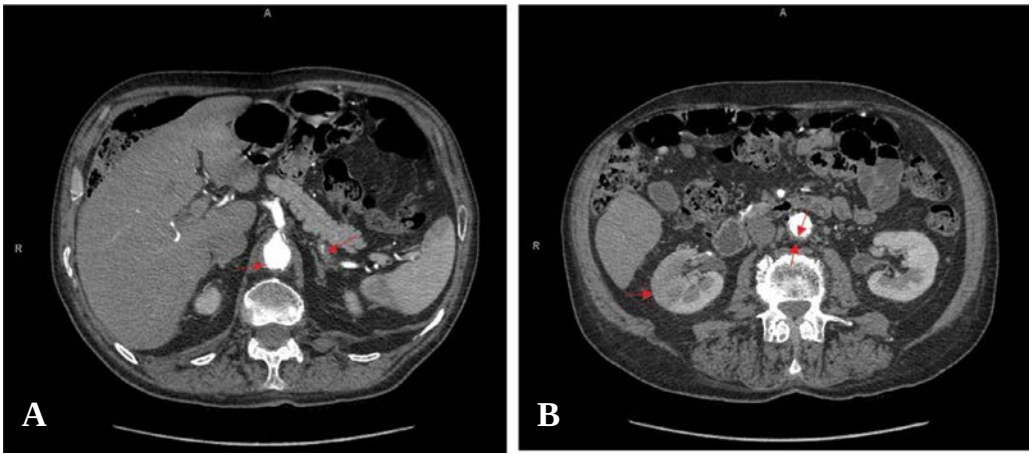

Figure 2. Computed tomography (CT) of the patient's abdomen at diagnosis. **A**, Segmental mural thickening of the splenic artery with significant narrowing of the lumen and aortitis of the abdominal aorta at the level of the celiac trunk is shown (**arrows**), with incomplete enhancement of splenic sinusoids during the arterial phase. **B**, Wall thickening of the infrarenal abdominal aorta on arterial phase imaging and ischemia of right renal parenchyma (**arrows**) was also demonstrated on CT.

Table 1. Laboratory test results for the patient, prior to treatment with steroids

Test	Result	Reference range
Leukocyte count, number/μl	9,500	4,000–10,000
Hemoglobin, gm/dl	10.8	13.5–17
Platelet count, number/μl	243,000	140,000–375,000
Erythrocyte sedimentation rate, mm/hour	93	0–15
C-reactive protein, mg/dl	3.81	0–0.8
Sodium, mEq/liter	131	135–145
Potassium, mEq/liter	4.7	3.8–5.1
Chloride, mEq/liter	95	97–109
Blood urea nitrogen, mg/dl	10	8–24
Creatinine, mg/dl	0.7	0.66–1.25
Aspartate aminotransferase, units/liter	10	0–40
Alkaline phosphatase, units/liter	90	30–120
Total bilirubin, mg/dl	1.1	0–1.0
Total protein, gm/dl	7.3	6.3–8.0
Albumin, gm/dl	3.9	3.4–4.5
Serum protein electrophoresis and immunofixation	No paraprotein detected	No paraprotein detected
Antinuclear antibody by indirect immunofluorescence assay	Negative	Negative
Anti–double-stranded DNA	<1 IU/ml	<4 IU/ml
Antibodies		
Anti-Smith	Negative	Negative
Anti-Ro	Negative	Negative
Anti-La	Negative	Negative
Anti–Jo-1	Negative	Negative
Anti–Scl-70	Negative	Negative
Anti–U1 RNP	Negative	Negative
Cryoglobulin	Negative	Negative
Antineutrophil cytoplasmic antibody screen	Negative	Negative
Complement C3, mg/dl	110	80–190
Complement C4, mg/dl	37.3	16–47
CH50 level, units/ml	>60	31–60
Quantitative IgG, mg/dl	1,179	694–1,618
IgG 1, mg/dl	717	382–929
IgG 2, mg/dl	281	241–700
IgG 3, mg/dl	42	22–178
IgG 4, mg/dl	58.5	40–86
Dilute Russell's viper venom time, seconds	Negative	Negative
Hexagonal phase phospholipid by neutralization assay	Negative	Negative
IgG anticardiolipin antibody	Negative	Negative
IgM anticardiolipin antibody	Negative	Negative
IgG anti–β^2-glycoprotein antibody	Negative	Negative
IgA anti–β^2-glycoprotein antibody	Negative	Negative
IgM anti–β^2-glycoprotein antibody	Negative	Negative
Hepatitis C antibody by enzyme immunoassay	Negative	Negative
Hepatitis B core antibody	Negative	Negative
Hepatitis B surface antigen	Negative	Negative
Rapid plasma reagin	Negative	Negative
Interferon-γ release–assay*	Indeterminate	Negative

* Tested after prednisone was given to the patient.

were clear in both lungs. There was no pericardial friction rub or murmur. Heart sounds were normal. No abdominal tenderness or organomegaly was observed. There was an abdominal bruit present on the left middle to lower quadrant. His carotid, brachial, radial, and femoral pulses were 2+. No rash was observed, and there was no joint tenderness or synovitis. The remaining results of the physical examination were unremarkable.

Laboratory evaluation

Laboratory studies prior to treatment with steroids are outlined in Table 1. The patient's ESR was 93 mm/hour (normal 0–15 mm/hour), and his C-reactive protein (CRP) level was 3.81 mg/dl (normal 0–0.8 mg/dl) prior to initiation of prednisone. His inflammatory markers had normalized after 2 weeks of prednisone to an ESR of 3 mm/hour and CRP level of <0.29 mg/dl. Radiographs of the chest did not show significant parenchymal disease. Transthoracic echocardiogram did not show any valvular abnormalities or vegetations.

CASE SUMMARY

A 70-year-old man was recently hospitalized due to hypertensive emergency from renal artery stenosis. Diagnostic evaluation revealed elevated ESR, and CT imaging of the abdomen showed thickening of both large- and medium-sized vessels.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of this case included diseases that manifest as primary or secondary vasculitides of large- to medium-sized vessels, IgG4-related disease, hereditary connective tissue diseases, infections, and vasculitis mimics (Table 2).

Primary or secondary large and medium vessel systemic vasculitis. Vasculitis involving large- and medium-sized vessels originating from diseases such as a systemic lupus erythematosus, rheumatoid arthritis, and Behçet's disease were excluded based on negative serologic test results and incompatible clinical presentation. Rare diseases associated with aortitis, such as relapsing polychondritis and Cogan's syndrome did not fit the clinical picture and usually spare medium-sized vessels.

There was an initial concern for polyarteritis nodosa due to the involvement of the renal artery branches and renal parenchymal ischemia. While the patient's visual disturbance is explained by medium vessel involvement, large vessel involvement displayed by the descending and abdominal aorta thickening was not consistent with this diagnosis. He also lacked the typical cutaneous manifestations or peripheral nerve involvement, such as mononeuritis multiplex, associated with medium vessel involvement.

Table 2. Differential diagnoses

Primary and secondary systemic vasculitis
Takayasu arteritis
Giant cell arteritis
IgG4-related disease
Ankylosing spondylitis
Systemic lupus erythematosus
Rheumatoid arthritis
Relapsing polychondritis
Cogan's syndrome
Polyarteritis nodosa
Sarcoidosis
Behçet's disease
Hereditary connective tissue disease
Vascular Ehlers-Danlos syndrome
Marfan syndrome
Loeys-Dietz syndrome
Infectious
Staphylococcus
Salmonella
Streptococcus
Pseudomonas
Mycobacterial and fungal infections
Vasculitis mimics
Fibromuscular dysplasia
Segmental arterial mediolysis
Atherosclerosis

IgG4-related disease. IgG4-related disease (IgG4-RD) is an immune-mediated systemic disease characterized by tissue infiltration by IgG4-positive plasma cells. Multiple organ systems are involved (1,2). Retroperitoneal fibrosis can occur involving the infrarenal aorta and can involve the iliac arteries. Aortitis and peri aortitis have also been described (3). Histopathologic findings of lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis with increased numbers of IgG4-positive plasma cells have been demonstrated (4). The patient lacked both the clinical and histopathologic findings that accompany this disease.

Hereditary connective tissue disease. Genetic disorders resulting in arterial aneurysms were lower in the differential since this was the patient's first presentation of such symptoms without any history of previous complications at a younger age (5). Ehlers-Danlos syndrome type IV, which is the vascular type of this condition (mutation of the type III procollagen *COL3A1*), was an unlikely cause of the patient's symptoms as he lacked the clinical manifestations of easy bruising, thin skin with visible veins, and characteristic facial features typically observed in this condition (6). Similarly, Marfan syndrome (mutation in the *FBN1* gene) and Loeys-Dietz syndrome (mutation in transforming growth factor β receptors 1 and 2) were also unlikely due to the patient's age, lack of family history, craniofacial features, or body habitus (7). Vascular complications in these disorders are due to vascular aneurysm, as opposed to vessel wall thickening leading to stenosis, which was observed in this patient. Additionally, individuals with these disorders do not present with such elevated markers of inflammation as seen in this patient.

Infection. Endocarditis was excluded due to the lack of constitutional symptoms, multiple sterile blood cultures, and a transthoracic echocardiogram that did not demonstrate any vegetations. Syphilis was excluded based on negative results from a rapid plasma reagin test. The patient had a positive result on a PPD skin test and indeterminate findings on interferon-γ–release assay. This infection had never been treated, which raised suspicion for tuberculosis. However, acid-fast bacilli were not identified in the sputum examination and his chest radiograph did not show

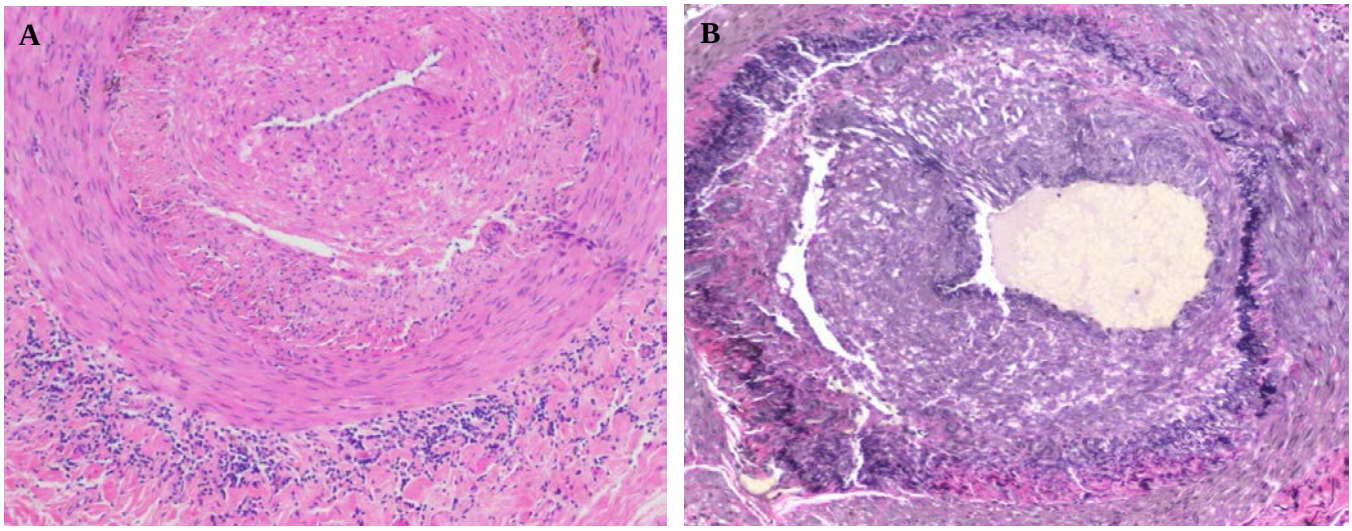

Figure 3. Images from a right and left temporal artery biopsy. **A**, Cross-sectional images of the temporal artery showing moderate-to-severe intimal thickening with compressed vascular lumen (top). A conspicuous lymphocytic infiltrate was present in the outer adventitial layer (bottom). **B**, Elastic tissue stain of the temporal artery showing a mostly destroyed and "moth-eaten" internal elastic lamina secondary to the lymphohistiocytic inflammation. A small remnant of normal internal elastic lamina was present (right). Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24164/abstract.

any pulmonary findings to suggest active tuberculosis or fungal infection. Additionally, vessel involvement is typically thought to be from a contiguous focus such as the lung, lymph node, or paraspinal abscess (8). This was not the case for this patient based on our investigations via imaging.

Vasculitis mimic. Segmental arterial mediolysis (SAM) and fibromuscular dysplasia (FMD) are noninflammatory vasculopathies that can present with dissection and a "string-of-beads" appearance with stenosis and narrowing of the involved arteries (9,10). Both can affect multiple vessels but primarily involve medium-sized vessels. SAM occurs most commonly in middle-aged men, whereas FMD has a predilection for women in their 20s and 30s (11). Both frequently involve abdominal vessels, but FMD also commonly involves the carotid and vertebral arteries. While this was an important consideration in this patient, the elevated markers of inflammation, the marked response to steroid, and large vessel involvement were not indicative of such disorders.

One of the most important differential diagnoses in this patient was that of atherosclerosis due to his age, history of alcohol abuse, and smoking history. Imaging features of concentric vessel wall thickening, number of vessels involved, and rapid progression over a short period of time did not support this diagnosis. Additionally, atherosclerosis has irregular eccentric plaques and typically occurs at branch points of vessels, which was not seen in this patient (12).

Takayasu arteritis and giant cell arteritis (GCA). Takayasu arteritis and GCA are large vessel vasculitides that share many overlapping features, such as aortic involvement and histopathologic features demonstrating granulomatous inflammation. Cranial symptoms such as headache, vision loss, jaw pain, and claudication are more predominant in GCA. Takayasu arteritis has a prevalence for aortic arch involvement with extremity claudication, hypertension, strokes, and arterial bruits. Typically, GCA occurs in older patients, whereas Takayasu arteritis is rare after age 50 years. As such, we favored GCA as the primary diagnosis as opposed to Takayasu arteritis, given the patient's age and cranial symptoms.

The patient was suspected to have GCA involving both cranial and extracranial vessels based on his age, the elevated ESR, features of headache, visual disturbance, dental (jaw) pain, and imaging results on CT.

CLINICAL COURSE

The patient underwent right and left temporal artery biopsy 3 weeks after prednisone initiation. Biopsy showed moderate lymphocytic infiltrate predominantly involving the adventitia layer and focally the muscular layer on both sides. There were very limited focal hemosiderin-laden macrophages. Focal necrosis and disruption of the elastic laminae was noted (Figure 3). Staining was negative for fungal organisms. No definite giant cells were seen, and biopsy failed to show the classic histopathologic feature of giant cells as biopsy was done after 3 weeks of steroid treatment. Unfortunately, the patient was lost to follow-up after his initial diagnosis and treatment.

One month after his biopsy, the patient was admitted to the hospital with gait ataxia and vision loss of the left eye. He reported stopping prednisone a few weeks earlier. Further evaluation revealed an elevated ESR of 75 mm/hour (normal 1–15 mm/hour) and CRP level of 6.09 mg/dl (normal 0–0.8 mg/dl). Results of an evaluation for infectious disease with cultures of sputum and blood were sterile. Acid-fast bacilli were not detected on sputum smear. Findings from a viral panel were unremarkable. Transthoracic echocardiogram did not show a vegetation or clot.

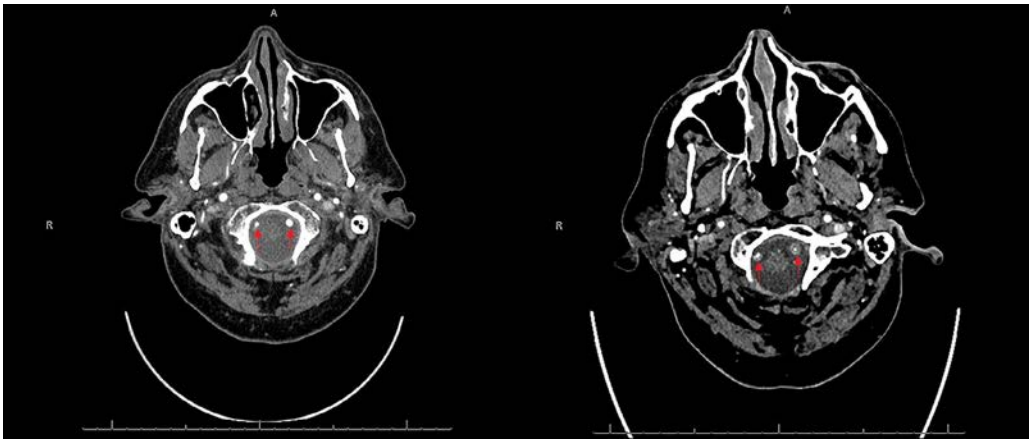

Figure 4. Computed tomography (CT) angiography of the patient's head and neck. Left, CT angiography of the head and neck 4 months prior to diagnosis. Normal vertebral arteries with left dominance (**arrows**) are indicated. Right, CT angiography of the head and neck of the patient performed during hospitalization for stroke after stopping prednisone. Thickening of the walls of the vertebral arteries, with pinpoint narrowing of the lumen of the dominant left vertebral artery, is demonstrated (**arrows**). Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24164/abstract.

CT imaging of the head without contrast showed a new area of hypoattenuation within the left brachium pontis with associated swelling representing acute to subacute infarction compared to a previous CT of the head performed a few months earlier. There was a new focus hypodensity within the right frontal corona radiata, which may represent infarct of an indeterminate age. CT angiography of the head and neck with contrast showed diffuse wall thickening of the aortic arch, bilateral subclavian arteries, common carotids, bilateral vertebral arteries, and internal carotid arteries. There was high-grade focal stenosis of the intracranial internal carotid arteries and left internal carotid artery ophthalmic segment. Although the patient had extensive atherosclerotic disease, the rapid progression of luminal stenosis over a 6-month period as evidenced by CT angiography of the head and neck was highly indicative of vasculitis (Figure 4). Accordingly, the patient received 1 gm of solumedrol daily for 3 days followed by a transition to 1 mg/kg of prednisone daily. The vision loss in his left eye did not improve despite receiving the high-dose steroid. Furthermore, ophthalmology examination showed evidence of arteritic anterior optic ischemic neuropathy involving the left eye. The patient was started on a regimen of isoniazid, vitamin B6, and rifapentine weekly due to positive testing for latent tuberculosis to prevent reactivation in the face of a prolonged prednisone course. Fortunately, his disease has remained in remission with normal ESR and no recurrence of the symptoms of his vasculitis, as he was compliant with receiving prednisone therapy.

DISCUSSION

Extracranial manifestations of GCA with large vessel involvement has been increasingly recognized in the literature. The thoracic and, to a lesser extent, abdominal aorta are the most involved vessels (13–15). However, renal artery involvement remains extremely rare (16). In a study conducted by Grayson et al, arteriographic lesions were identified using magnetic resonance angiography (MRA) in patients with GCA and Takayasu arteritis. Among those individuals with GCA, 8% had left renal involvement and 16% had right renal involvement (17). Another study found that in 120 patients with GCA, 11% of patients had right renal artery involvement and 5% had left renal artery involvement as evidenced by imaging modalities (18). In both of the abovementioned studies, clinical features were not described. A retrospective study looking at 18 patients above the age of 50 years who had large vessel arteritis on imaging (MRA, CTA, or intravenous angiography) showed 3 patients with renal involvement. Within this cohort, 3 patients presented with new-onset hypertension, and 10 patients also had cranial symptoms (19). Renal failure in patients with GCA has also been described in a few case reports but not because of renal artery stenosis (20–24). Moreover, the patient treated at our clinic had preserved renal function. Those individuals with GCA and prominent symptoms derived from stenosing large vessel involvement tend to have a lower frequency of cranial symptoms (25). The patient had both cranial and extracranial symptoms with renal artery involvement, which is rarely reported in the literature.

The draft classification criteria for GCA presented at the 2018 American College of Rheumatology/Association of Rheumatology Professionals annual meeting recognizes bilateral axillary involvement and aortic involvement as seen on fluorodeoxyglucose–positron emission tomography as part of the classification for GCA. However, abdominal aorta with renal or mesenteric involvement was included in the classification criteria for Takayasu arteritis and absent from the GCA classification criteria. The classification criteria for large vessel vasculitis also reinforced that patients must be less than 60 years old to be diagnosed with Takayasu arteritis (26). Here, we present a case of GCA in a 70-year-old male patient with cranial, extracranial, mesenteric, renal, pelvic, and aortic (supra and infrarenal) vasculitic involvement.

Strokes in the territory of the carotid artery or the vertebrobasilar artery are more frequently seen in Takayasu arteritis and are rarely reported in GCA (27). The patient had a profound ischemic cerebrovascular accident involving multiple vascular territories including the vertebrobasilar artery as seen in his CTA, which was normal a few months prior to diagnosis. Strokes, especially in the vertebrobasilar territory, are more likely to occur in patients with GCA who experience recent ophthalmic ischemic symptoms (28). Frequent relapses were also noted in a recent retrospective observational analysis of 8 biopsy-proven GCA patients with bilateral distal involvement of the vertebral and basilar arteries (29).

Perhaps the most striking features of this case are the unusual extensive involvement of aortic branches and the rapid progression of intraluminal stenosis of the cranial arteries over a short period of time as shown in Figure 1. Decreased survival is seen in individuals with GCA associated with aortic aneurysm and dissection, particularly 5 years after the diagnosis (30–32), which further warrants prompt diagnosis and treatment.

FINAL DIAGNOSIS

Cranial and extracranial GCA with rare features of renal artery involvement leading to hypertensive crisis, which then progressed to an ischemic stroke involving the vertebrobasilar and carotid artery territories.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Sharmeen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Sharmeen, Arcomano, Langenberg, Kato, Allam.

Acquisition of data. Sharmeen, Arcomano, Langenberg, Kato, Allam.

Analysis and interpretation of data. Sharmeen, Arcomano, Langenberg, Kato, Allam.

REFERENCES

1. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol 2012;22:1–14.
2. Neild GH, Rodriguez-Justo M, Wall C, OConolly JO. Hyper-IgG4 disease: report and characterisation of a new disease. BMC Med 2006;4:23.
3. Stone JR. Aortitis, periaortitis, and retroperitoneal fibrosis, as manifestations of IgG4-related systemic disease. Curr Opin Rheumatol 2011;23:88.
4. Khosroshahi A, Stone JH. A clinical overview of IgG4-related systemic disease. Curr Opin Rheumatol 2011;23:57–66.
5. Skeik N, Hyde JR, Olson SL, Thaler CM, Abuatiyeh W, Ahmed AK, et al. Nonatherosclerotic abdominal vasculopathies. Ann Vasc Surg 2019;60:128–46.
6. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med 2000;342:673–80.
7. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355:788–98.
8. Long R, Guzman R, Greenberg H, Safneck J, Hershfield E. Tuberculous mycotic aneurysm of the aorta: review of published medical and surgical experience. Chest 1999;115:522–31.
9. Slavin RE, Saeki K, Bhagavan B, Maas AE. Segmental arterial mediolysis: a precursor to fibromuscular dysplasia? Mod Pathol 1995;8:287–94.
10. Tan R. Segmental arterial mediolysis: a case study and review of the literature in accurate diagnosis and management. Vasc Specialist Int 2019;35:174–9.
11. Kalva SP, Somarouthu B, Jaff MR, Wicky S. Segmental arterial mediolysis: clinical and imaging features at presentation and during follow-up. J Vasc Interv Radiol 2011;22:1380–7.
12. Gotway MB, Araoz PA, Macedo TA, Stanson AW, Higgins CB, Ring EJ, et al. Imaging findings in Takayasu's arteritis. AJR Am J Roentgenol 2005;184:1945–50.
13. Agard C, Barrier JH, Dupas B, Ponge T, Mahr A, Fradet G, et al. Aortic involvement in recent-onset giant cell (temporal) arteritis: a case-control prospective study using helical aortic computed tomodensitometric scan. Arthritis Rheum 2008;59:670–6.
14. Blockmans D, De Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive ^{18}F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. Arthritis Rheum 2006;55:131–7.
15. Walter MA, Melzer RA, Schindler C, Müller-Brand J, Tyndall A, Nitzche E. The value of [^{18}F]FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease. Eur J Nucl Med Mol Imaging 2005;32:674–81.
16. Lensen KD, Voskuyl AE, Comans EF, van der Laken CJ, Smulders YM. Extracranial giant cell arteritis: a narrative review. Neth J Med 2016;74:182–92.
17. Grayson PC, Maksimowicz-McKinnon K, Clark TM, Tomasson G, Cuthbertson D, Carette S, et al. Distribution of arterial lesions in Takayasu's arteritis and giant cell arteritis. Ann Rheum Dis 2012;71:1329–34.
18. Aschwanden M, Kesten F, Stern M, Thalhammer C, Walker UA, Tyndall A, et al. Vascular involvement in patients with giant cell arteritis determined by duplex sonography of 2x11 arterial regions. Ann Rheum Dis 2010;69:1356–9.
19. Polachek A, Pauzner R, Levartovsky D, Rosen G, Nesher G, Breuer G, et al. The fine line between Takayasu arteritis and giant cell arteritis. Clin Rheumatol 2015;34:721–7.
20. Medvedev G, Al-Shamari AE, Copland MA, Magil AB. Isolated renal giant cell arteritis. Am J Kidney Dis 2002;40:658–61.
21. Lenz T, Schmidt R, Scherberich JE, Gröne HJ. Renal failure in giant cell vasculitis. Am J Kidney Dis 1998;31:1044–7.
22. Truong L, Kopelman RG, Williams GS, Pirani CL. Temporal arteritis and renal disease. Am J Med 1985;78:171–5.
23. Canton CG, Bernis C, Paraiso V, Barril G, García A, Osorio C, et al. Renal failure in temporal arteritis. Am J Nephrol 1992;12:380–3.
24. Govil YK, Sabanathan K, Scott D. Giant cell arteritis presenting as renal vasculitis. Postgrad Med J 1998;74:170–1.
25. Cid MC, Prieto-González S, Arguis P, Espígol-Frigolé G, Butjosa M, Hernández-Rodríguez J, et al. The spectrum of vascular involvement in giant-cell arteritis: clinical consequences of detrimental vascular remodeling at different sites. APMIS Suppl 2009;127:10–2.
26. Merkel PA, Unizony S, Ponte C, Grayson PC, Suppiah P. Updated classification criteria for large vessel vasculitis. Presented at American College of Rheumatology/Association of Rheumatology Professionals Annual Meeting; 2018 October 19–24; Chicago, Illinois.
27. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Gomez-Acebo I, Pego-Reigosa R, Lopez-Diaz MJ, Vazquez-Triñanes MC, et al. Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. Medicine (Baltimore) 2009;88:227–35.
28. De Boysson H, Liozon E, Larivière D, Samson M, Parienti JJ, Boutemy J, et al. Giant cell arteritis–related stroke: a retrospective multicenter case-control study. J Rheumatol 2017;44:297–303.
29. Larivière D, Sacre K, Klein I, Hyafil F, Choudat L, Chauveheid MP, et al. Extra- and intracranial cerebral vasculitis in giant cell arteritis: an observational study. Medicine (Baltimore) 2014;93:e265.
30. Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant cell arteritis. N Engl J Med 2002;347:261–71.
31. De Boysson H, Daumas A, Vautier M, Parienti JJ, Liozon E, Lambert M, et al. Large-vessel involvement and aortic dilation in giant-cell arteritis: a multicenter study of 549 patients. Autoimmun Rev 2018;17:391–8.
32. Kermani TA, Warrington KJ, Crowson CS, Ytterberg SR, Hunder GG, Gabriel SE, et al. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. Ann Rheum Dis 2013;72:1989–94.

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CLINICOPATHOLOGIC CONFERENCE

Straight From the Cradle: A Patient With Early-Onset Polyautoimmunity and Recurrent Infections

Samuel Gaine,[1] Diana M. Bongiorno,[2] Sara Baig,[3] Andrea Fava,[2] and George Stojan[2]

CASE PRESENTATION

Chief symptoms

A 29-year-old man presented with fever, shortness of breath, a productive cough, and worsening rash.

History of the present illness

A Caucasian man with a history of autoimmune hepatitis who was receiving chronic prednisone therapy developed a rash over his chest, back, and upper extremities. The patient was evaluated by a dermatologist who thought his scattered and ill-defined erythematous patches were consistent with an eczema flare. Topical steroids were prescribed.

The following month, the patient developed shortness of breath and a productive cough. He was diagnosed as having the influenza B virus and completed a course of oseltamivir. Shortness of breath worsened, and the patient developed a fever, prompting him to present to the emergency department.

Computed tomography (CT) without contrast of the chest showed bilateral peribronchovascular nodules with air bronchograms, diffuse centrilobular nodularity, bilateral tree-in-bud nodularity within the lower lobes, and extensive hilar and mediastinal lymphadenopathy, with the largest nodes measuring up to 1.9 cm (Figure 1). Abdominal adenopathy with mild splenomegaly was noted.

A bronchoscopy was performed. Aspiration of the lymph node revealed benign lymphoid tissue and respiratory epithelium without evidence of malignancy. Cytopathology findings showed normal lymphoid tissue, and flow cytometry results were unrevealing. Bronchoalveolar lavage cultures showed no evidence of viral, bacterial, fungal, or mycobacterial infection. The patient then underwent a video-assisted thoracoscopic surgery/mediastinoscopy with resection of multiple pulmonary nodules and biopsy of an enlarged paratracheal lymph node. Histopathologic analysis of the lung showed 2 dominant patterns: 1) dense lymphoplasmacytic infiltrates within the interstitium with variable interstitial fibrosis and without any well-defined granulomas that were consistent with a nonspecific interstitial pneumonia (NSIP) pattern and 2) sheets of intraalveolar macrophages, which is a pattern seen with desquamative interstitial pneumonia but is commonly described in immunosuppressed patients with infectious pneumonia ("histiocytic pneumonia") (1). Pulmonary function tests showed a restrictive pattern and moderate impairment of carbon monoxide diffusion supportive of a diagnosis of interstitial lung disease (ILD). Moxifloxacin was started for management of suspected pneumonia in the patient.

A skin biopsy of the rash showed perivascular and interstitial dermal mixed infiltrate with neutrophils, eosinophils, leukocytoclasia, and perivascular fibrin with no specific immune deposits seen on direct immunofluorescence staining using conjugates specific for IgG, IgA, IgM, C3, and fibrin. While histopathologic analysis was not diagnostic of urticarial vasculitis, the presence of perivascular inflammatory infiltrates combined with perivascular nuclear dust (leukocytoclasia) were thought to be atypical for simple urticaria, so an urticarial vasculitis was considered a more likely diagnosis. The rheumatology department was consulted out of concern for an underlying autoimmune disease in the patient.

Medical history

In the first year of his life, the patient had recurrent upper respiratory infections. At age 2 years old, he developed jaundice, and a biopsy of the liver confirmed a diagnosis of autoimmune hepatitis for which he started receiving prednisone monotherapy. Azathioprine at a dose of 150 mg daily was added to the patient's regimen when he was 18 years old. Six years later, azathioprine was discontinued after he developed multifocal basal cell carcinoma of the nose, which required resection and reconstruction.

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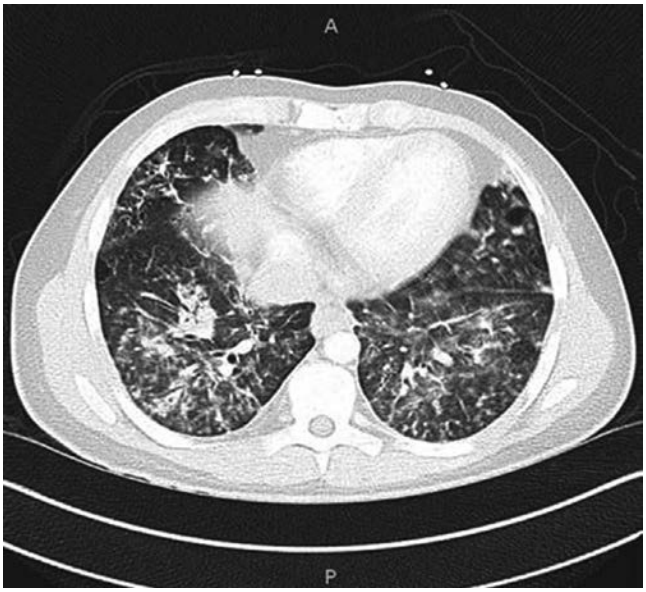

Figure 1. Computed tomography of the chest showing bilateral patchy and confluent ground-glass opacities and consolidative abnormalities consistent with a diagnosis of nonspecific interstitial pneumonia.

Over the years, the patient continued to have recurrent upper respiratory, sinus, and middle ear infections while receiving chronic glucocorticoids for autoimmune hepatitis. He was also diagnosed as having autism spectrum disorder. During adolescence, he was noted to have a short stature.

At age 26, his liver function tests were noted to be elevated with an aspartate transaminase (AST) level of 65 units/liter, alanine aminotransferase (ALT) level of 110 units/liter, and alkaline phosphatase (AP) level of 126 units/liter. A liver biopsy showed chronic hepatitis with mild activity and stage III fibrosis. Based on these findings, prednisone therapy was increased to 20 mg daily for a period of time. Despite chronic evidence of transaminitis, the patient did not develop any evidence of hepatic dysfunction or failure. He was diagnosed with splenomegaly at age 23 years old, but there was no evidence of hepatomegaly until age 29 years old.

Medications

The patient's medication list at the time of the current admission included 10 mg of prednisone daily, topical triamcinolone 0.1% for the rash, 150 mg of bupropion daily, 20 mg of esomeprazole daily, 75 mg of sertraline daily, and 10 mg of montelukast daily. The patient used albuterol inhalers as needed for shortness of breath and docusate for constipation.

Social and family history

There was no family history of autoimmune or rheumatic disorders. The patient did not have any personal history of alcohol or substance use. He had a half pack of cigarettes per year smoking history but had stopped smoking cigarettes three years prior to this hospital admission. The patient was a business school graduate and was unemployed at the time of admission.

Physical examination

The patient's vital signs were within normal limits. He was lying in bed comfortably without any acute distress. The patient's bedside sputum container was noted to contain thick, blood-tinged green sputum. He had mild clubbing on examination. There was evidence of moon facies and buffalo hump, as well as a scar on the patient's nasal ridge at the site of a basal cell carcinoma excision.

Findings on skin examination were significant for a diffuse erythematous papular rash that coalesced into plaques over the patient's anterior chest and bilateral upper extremities (Figure 2). Multiple hyperkeratotic flat erythematous plaques were present on the dorsum of the metacarpophalangeal and interphalangeal joints (Figure 3). A few periorbital petechiae were noted, which were attributed to intensive bouts of coughing. Lung auscultation revealed bilateral inspiratory crackles, which were worse on the right side. Heart rate and rhythm were normal. No murmurs, rubs, or gallops were noted on auscultation. A comprehensive musculoskeletal examination was remarkable for absence of any synovitis. Neurologic examination showed 5/5 strength in the proximal and distal muscles of the upper and lower extremities. Reflexes were 2/4 throughout. Babinski's sign was not elicited. Sensory examination was normal to touch, temperature, and pinprick sensation in all of the patient's extremities.

Laboratory evaluation

The patient's laboratory results demonstrated a normal white blood cell (WBC) count of 8.6/mm^3, hemoglobin level of of 11.6 gm/dl, and a normal platelet count of 277,000/mm^3 (Table 1). Creatinine level was 0.7 mg/dl with normal electrolyte levels, including calcium. Liver function tests showed slight elevations in AP (124 units/liter), ALT (52 units/liter), and levels of total bilirubin (1.4 mg/dl). Serum protein electrophoresis findings and vitamin B12, creatine kinase, and lactate dehydrogenase levels were within normal limits. Urinalysis results were unremarkable.

Serologic testing indicated positive results for anti–smooth muscle antibody and direct antiglobulin test (Coombs' test). Antinuclear antibodies were negative. U1/2-RNP, Jo-1, Ku, OJ, PL-12, PL-7, PM-Scl, Ro, SRP, Mi-2, and double-stranded DNA antibodies were not detected. Serologic test results for Epstein-Barr virus and cytomegalovirus were negative. Complement C3 and C4 levels were normal. An immunoglobin panel showed an elevated IgM level of 365 mg/dl, and analysis of IgG subsets was notable for an undetectable IgG4 value.

Flow cytometry analysis showed elevated CD19+ lymphocytes, but lymphocyte subset analysis did not reveal

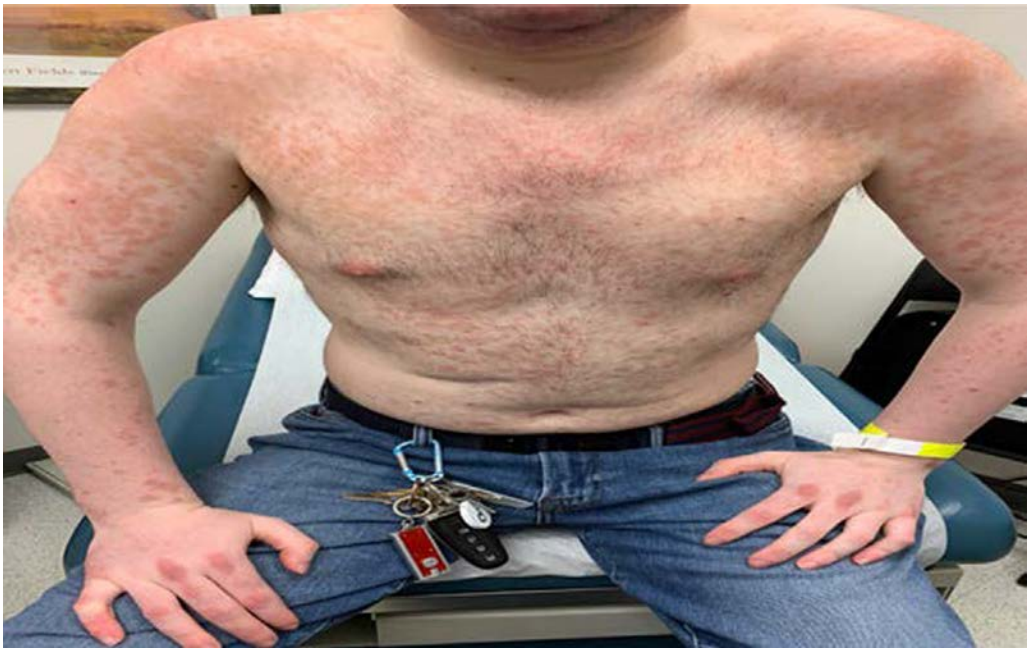

Figure 2. Diffuse erythematous papular rash of the chest and upper extremities with the presence of Gottron's papules of the knuckles.

double-negative T cells. Soluble FasL, interleukin-10 (IL-10), and IL-18 plasma levels were not elevated in the patient.

CASE SUMMARY

A 29-year-old man with a history of recurrent infections since birth, autoimmune hepatitis, NSIP with dense lymphoplasmacytic infiltrate, positive direct Coombs' test, diffuse mediastinal lymphadenopathy, hepatomegaly, and splenomegaly presented with pneumonia related to influenza B infection and urticarial vasculitis.

DIFFERENTIAL DIAGNOSIS

The main question to address in this patient with a complex medical history was whether a unifying syndrome could explain all of the manifestations that he had been experiencing since birth. A systemic autoimmune disease was suspected based on his history of autoimmune hepatitis, NSIP, urticarial vasculitis, Gottron's papules, and direct Coombs' test. However, onset of the first manifestation at age 2 years, with sequential accumulation of new autoimmune features over the years, was unusual. In the context of his early-onset recurrent infections and bulky lymphadenopathy, a genetic disease was suspected.

The main autoimmune diseases that were considered in our differential included amyopathic dermatomyositis, given the presence of Gottron's papules, as well as systemic lupus erythematosus due to his direct Coombs' test and multiple organ involvement.

Opportunistic infections were considered due to the patient's history of recurrent infections and long-term immunosuppression.

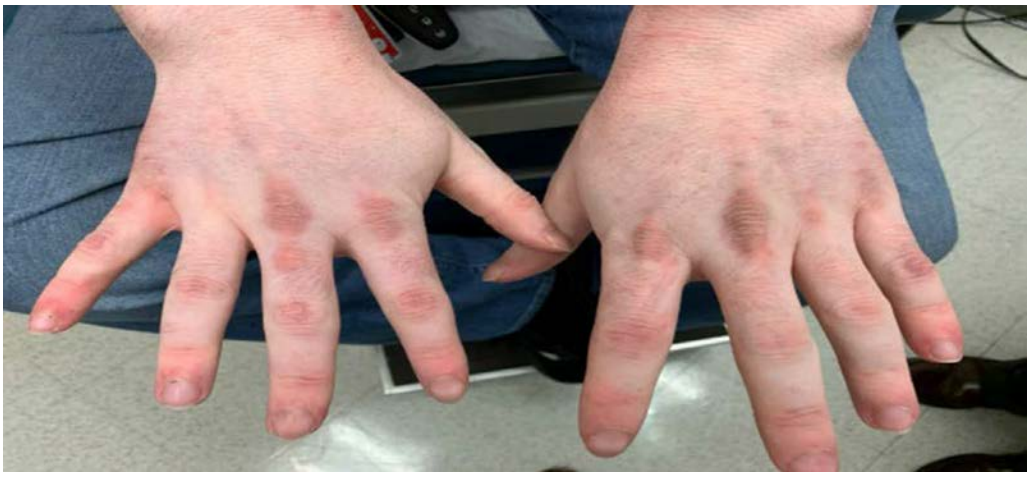

Figure 3. Gottron's papules on the dorsum of the metacarpophalangeal and interphalangeal joints of the patient's hands.

Table 1. Laboratory data*

Test	Result
Clinical tests	
WBC, mm^3	8.6
Hemoglobin, gm/dl	11.6
Platelet count, mm^3	277,000
AP, units/liter	124
ALT, units/liter	52
Total bilirubin, mg/dl	1.4
Creatinine, mg/dl	0.7
Creatine kinase, units/liter	34
LDH, units/liter	183
C3, mg/dl	100.1
C4, mg/dl	16.32
Vitamin B12, pg/ml	584
Antibodies	
ASMA	Positive
Coombs	Positive
ANA	Negative
Anti–U1/U2 RNP	Negative
Jo-1	Negative
Ku	Negative
OJ	Negative
PL-12	Negative
PL-7	Negative
PM-Scl	Negative
Ro	Negative
SRP	Negative
Mi-2	Negative
Double-stranded DNA	Negative
Viral serologic testing	
EBV	Negative
CMV	Negative
Immunoglobins, mg/dl	
IgM	365
IgE	<0.2
IgG1	404
IgG2	547
IgG3	128.5
IgG4	0.8
Flow cytometry	
CD19+ lymphocytes	Elevated
Double-negative T cells	None
Soluble FasL	Not elevated
IL-10	Not elevated
IL-18	Not elevated

* ALT = alanine aminotransferase; ANA = antinuclear antibody; AP = alkaline phosphatase; ASMA = anti–smooth muscle antibody; CMV = cytomegalovirus; EBV = Epstein-Barr virus; IL-10 = interleukin-10; LDH = lactate dehydrogenase; SRP = signal recognition particle; WBC = white blood cell count.

Extensive evaluation over several years, including bronchoscopy and lymph node biopsy, however, revealed no evidence of an underlying infection. The patient's recent influenza B infection had likely resulted in a reactive increase in his lymphadenopathy.

The presence of bulky lymphadenopathy and splenomegaly for several years with an unremarkable lymph node biopsy and flow cytometry analysis were strong arguments that this was a nonmalignant process. However, the threshold for repeating a lymph node biopsy to rule out malignant transformation remained low.

Recurrent childhood infections suggested a primary immunodeficiency, although the patient's chronic glucocorticoid exposure may have been an important risk factor for these frequent infections. While he had an undetectable IgG4, this was unlikely to be the primary factor contributing to recurrent infections. A range of inherited immunodeficiency syndromes were considered, particularly those associated with chronic lymphoproliferation and polyautoimmune disease. A question arose about the possibility of common variable immune deficiency. Some subgroups of patients with common variable immune deficiency experience lymphoproliferation and various forms of autoimmune disease (2). Recurrent infections and autoimmune cytopenia are both commonly found in certain subtypes of hyper IgM syndrome, and the patient was noted to have an elevated concentration of serum IgM (3).

We considered autoimmune lymphoproliferative syndrome (ALPS). ALPS is characterized by lymphoproliferative disorders, autoimmune disease, and an increased risk of lymphoma, typically due to mutations in the FAS signaling pathway leading to impaired apoptosis (4). Lymphadenopathy is almost universally present. Splenomegaly and hepatomegaly are very common findings (4). In addition, autoimmune hepatitis with an early onset can be a presenting feature of ALPS. Hemolytic anemia is probably the most common autoimmune manifestations of this syndrome, and our patient had a positive result on direct Coombs' test (5). The lack of double-negative T cells on peripheral flow cytometry argued against ALPS as the underlying diagnosis, but an ALPS-like disorder was still suspected.

Patients with mutations in the *LRBA* gene can present with lymphadenopathy, splenomegaly, and autoimmune hemolytic anemia; however, patients may also have elevated double-negative T cells and elevated FasL, neither of which was seen in the patient (6).

Another differential diagnosis to consider was COPA syndrome, a novel monogenetic autosomal dominant autoimmune disease (7,8). While the patient had ILD in an NSIP pattern, which can be seen in COPA syndrome, he had no evidence of inflammatory arthritis or glomerulonephritis, which are typical clinical manifestations in this syndrome (9).

CLINICAL COURSE

Whole-genome sequencing revealed that the patient was heterozygous for a gain-of-function germline mutation of STAT3. No somatic mutations in Fas, FasL, or CASP10 were detected. History of recurrent infections, generalized lymphadenopathy, splenomegaly, and various autoimmune manifestations (autoimmune hepatitis, NSIP, urticarial vasculitis, direct Coombs) in the setting of the likely pathogenic STAT3 variant was consistent with a diagnosis of STAT3 gain-of-function syndrome.

In the acute care setting, the patient was treated with an oral glucocorticoid taper, and he was continued on low-dose prednisone in the outpatient setting. He underwent an extensive evaluation posthospitalization for possible underlying

inflammatory myopathy with no myositis-specific or myositis-associated autoantibodies detected and with no evidence of myopathy. Once a diagnosis of STAT3 gain-of-function syndrome was firmly established, the initiation of tofacitinib therapy was planned in coordination with his outpatient rheumatologist. Fortunately, both the patient's autoimmune hepatitis and ILD have remained stable since his hospitalization.

DISCUSSION

STAT3 gain-of-function syndrome is a rare genetic syndrome caused by heterozygous STAT3 gain-of-function germline mutations that typically present with failure to thrive, early-onset solid-organ autoimmunity, autoimmune cytopenias, lymphoproliferation, and increased susceptibility to infections (10,11). Disease onset typically occurs very early, with >40% of patients presenting with symptoms within the first year of life (10). Twenty-eight different mutations have been described in the STAT3 signaling pathway to date, leading to a diverse clinical phenotype, which presents a difficult diagnostic challenge (10).

Hematologic manifestations are frequent and include lymphoproliferation (adenopathy and hepatosplenomegaly), immunodeficiency (hypogammaglobulinemia), and autoimmune cytopenias (10). Patients usually have a greater susceptibility to infection, especially recurrent respiratory tract infections, secondary to hypogammaglobulinemia. Elevated levels of IgM, which was present in the patient, is not a typical manifestation of STAT3 gain-of-function disease, but it has been described in a few cases (12). The exact mechanism leading to the IgM elevation is unknown. Lymphoproliferation is common, and in a recent systematic review, about 80% of patients had chronic lymphoproliferation as early as 6 months of age (10). These findings were consistent with the patient's past medical history.

Gastrointestinal disease typically presents in the first year of life with diarrhea and failure to thrive secondary to enteropathy, which is classically described as pseudoceliac disease with duodenal villous atrophy and intraepithelial lymphocyte infiltration, but without favorable response to a gluten-free diet (10). Autoimmune hepatitis was reported in 10% of patients, 2 of whom required a liver transplant (10).

ILD typically occurs in the teenage years and has been reported in 30% of patients (10). Lymphocytic interstitial pneumonitis and desquamative interstitial pneumonitis are some of the most commonly seen histopathologic categories. Diffuse interstitial fibrosis is rarely present. Most patients require prolonged immunosuppression, but respiratory insufficiency is rare.

Type 1 diabetes mellitus tends to occur in first few weeks of life and is the most common endocrinopathy (10). Failure to thrive and short stature are commonly multifactorial in etiology and may be related to frequent infections, autoimmunity, enteropathy, and/or hypopituitarism.

Multiorgan autoimmune disease is seen in ~75% of patients and usually encompasses arthritis, autoimmune hepatitis, pseudoceliac disease, ILD, and autoimmune cytopenia (10,13). Vasculitis is a rare manifestation, with only a single case report of microscopic polyangiitis described in the literature to our knowledge (14). There are no previous cases describing individuals with STAT3 gain-of-function syndrome as having urticarial vasculitis. Similarly, inflammatory myopathies or cutaneous manifestations of dermatomyositis have not been described previously, underlying the unique presentation of the patient.

Since ALPS shares many features with STAT3 gain-of-function disease, we considered the differences between these two rare conditions. As ALPS is the more widely known of the autoimmune/lymphoproliferative disorders, it was high on our initial differential diagnosis. However, ALPS typically is not characterized by a normal number of double-negative T cells or lymphoproliferative infiltration of the lungs or other non-lymphoid organs, so when these features are present, testing for an alternative genetic condition can be considered (12).

STAT3 is a critical transcription factor in the immune response, especially in Th17 cells. It can be directly targeted by JAK/STAT inhibitors such as tofacitinib, which was the medication that the team planned to start for the patient once a diagnosis was confirmed. Since STAT3 is implicated in IL-6 receptor signalling, IL-6 inhibitors have also been used successfully (10).

Widespread availability of genetic sequencing will likely aid in the early detection of STAT3 gain-of-function disease and genetic variants (12,15). In this patient, the clinical presentation was typical for STAT3 gain-of-function syndrome. However, interpretation of laboratory studies and clinical manifestations may be complicated by long-term use of systemic immunosuppressants, including glucocorticoids, which may be prescribed for many years prior to diagnosis (10).

Our case highlighted the need to always consider genetic causes when autoimmunity presents at a very early age. Monogenetic disorders facilitate unique insights into the pathogenesis of autoimmune conditions, and the precise diagnosis of a genetic defect may lead to specific and impactful treatments, and appropriate monitoring.

FINAL DIAGNOSIS

STAT3 gain-of-function syndrome.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Gaine had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Gaine, Fava, Stojan.
Acquisition of data. Gaine, Bongiorno, Baig, Fava, Stojan.
Analysis and interpretation of data. Gaine, Bongiorno, Stojan.

REFERENCES

1. Leslie KO. My approach to interstitial lung disease using clinical, radiological and histopathological patterns. J Clin Pathol 2009;62:387–401.
2. Salzer U, Warnatz K, Peter HH. Common variable immunodeficiency: an update [review]. Arthritis Res Ther 2012;14:223.
3. Imai K, Catalan N, Plebani A, Maródi L, Sanal Ö, Kumaki S, et al. Hyper-IgM syndrome type 4 with a B lymphocyte–intrinsic selective deficiency in Ig class-switch recombination. J Clin Invest 2003;112:136–42.
4. Matson DR, Yang DT. Autoimmune lymphoproliferative syndrome: an overview. Arch Pathol Lab Med 2020;144:245–51.
5. Bride K, Teachey D. Autoimmune lymphoproliferative syndrome: more than a FAScinating disease [review]. F1000Res 2017;6:1928.
6. Revel-Vilk S, Fischer U, Keller B, Nabhani S, Gámez-Díaz L, Rensing-Ehl A, et al. Autoimmune lymphoproliferative syndrome-like disease in patients with LRBA mutation. Clin Immunol 2015; 159:84–92.
7. Patwardhan A, Spencer CH. An unprecedented COPA gene mutation in two patients in the same family: comparative clinical analysis of newly reported patients with other known COPA gene mutations [review]. Pediatr Rheumatol 2019;17:59.
8. Watkin LB, Jessen B, Wiszniewski W, Vece TJ, Jan M, Sha Y, et al. COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis. Nat Gen 2015;47:654–60.
9. Vece TJ, Watkin LB, Nicholas SK, Canter D, Braun MC, Guillerman RP, et al. Copa syndrome: a novel autosomal dominant immune dysregulatory disease. J Clin Immunol 2016;36:377–87.
10. Fabre A, Marchal S, Barlogis V, Mari B, Barbry P, Rohrlich PS, et al. Clinical aspects of STAT3 gain-of-function germline mutations: a systematic review. J Allergy Clin Immunol Pract 2019;7:1958–69.e9.
11. Flanagan SE, Haapaniemi E, Russell MA, Caswell R, Allen HL, De Franco E, et al. Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease. Nat Genet 2014;46:812–4.
12. Weinreich MA, Vogel TP, Rao VK, Milner JD. Up, down, and all around: diagnosis and treatment of novel STAT3 Variant. Front Pediatr 2017;5:49.
13. Velayos T, Martínez R, Alonso M, Garcia-Etxebarria K, Aguayo A, Camarero C, et al. An activating mutation in STAT3 results in neonatal diabetes through reduced insulin synthesis. Diabetes 2017;66:1022–9.
14. Sachs JW, Miller HK, Wright BL, Bauer CS. Contrasting clinical presentations in brothers with identical STAT3 gain-of-function mutations. J Allergy Clin Immunol Pract 2019;143:AB114.
15. Jägle S, Heeg M, Grün S, Rensing-Ehl A, Maccari ME, Klemann C, et al. Distinct molecular response patterns of activating STAT3 mutations associate with penetrance of lymphoproliferation and autoimmunity. Clin Immunol 2020;210:108316.

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Variation in Treatment of Children Hospitalized With New-Onset Systemic Juvenile Idiopathic Arthritis in the US

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Objective. Increasing evidence supports the conclusion that early initiation of biologics may dramatically improve disease course and reduce glucocorticoid exposure for children with systemic juvenile idiopathic arthritis (JIA). The present study was undertaken to characterize variation in the use of first-line biologic and glucocorticoid therapy and to identify drivers of variation in children hospitalized with new-onset systemic JIA.

Methods. We conducted a retrospective cohort study of children hospitalized with new-onset systemic JIA from 2008 to 2019 utilizing a comparative pediatric database from 52 tertiary care children's hospitals. Subjects and treatment receipt were identified using International Classification of Diseases, Ninth Revision (ICD-9) and ICD-10 discharge diagnosis codes, pharmacy billing data, and clinical transaction classification codes. Mixed-effects logistic regression was used to identify patient- and hospital-level factors associated with receipt of glucocorticoids and biologics.

Results. In total, 534 children with new-onset systemic JIA hospitalized during the study period met inclusion criteria. Twenty-nine percent received biologics, and 58% received glucocorticoids. Biologic use increased over time ($P < 0.001$), methotrexate use decreased ($P < 0.01$), and glucocorticoid use remained unchanged. Biologics and glucocorticoid use varied significantly between hospitals. High annual hospital volume, intensive care unit stay, and later discharge year were significantly associated with biologic exposure. Medium-high and high annual hospital volume were significantly associated with less glucocorticoid exposure.

Conclusion. Despite increasing evidence demonstrating improved outcomes with first-line treatment with biologics, we found significant treatment variation across hospitals with many children not receiving biologics and a persistent high rate of glucocorticoid exposure. These results underscore the need for comparative efficacy studies and improved treatment standardization.

INTRODUCTION

Systemic juvenile idiopathic arthritis (JIA) is an autoinflammatory condition with a very distinct clinical phenotype from other subtypes of JIA, characterized by daily high-spiking fevers, evanescent rashes, hepatosplenomegaly, lymphadenopathy, and serositis. These systemic disease manifestations are often more prominent than arthritis, which can present weeks to months later in the disease course. Management approaches for patients with new-onset systemic JIA have historically included the use of glucocorticoids. In 2012, multiple randomized controlled trials demonstrated efficacy of interleukin-1 (IL-1) and IL-6 inhibitors (biologics) in treating both the systemic and articular manifestations of systemic JIA, leading to more widespread use and improved outcomes (1–3). With the availability of more diverse therapeutic options, provider self-reports indicate significant variation in treatment of patients with new-onset systemic JIA (4).

Increasing evidence continues to emerge suggesting that early initiation of biologics may dramatically improve disease course and reduce glucocorticoid exposure (5). However, the frequency of first-line biologic use and temporal trends in treatment of patients with new-onset systemic JIA are not known. In order to move toward a more standardized therapeutic approach, it is first necessary to characterize treatment variation in a real-world

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SIGNIFICANCE & INNOVATIONS

- This study is the largest cohort to evaluate treatment of hospitalized patients with new-onset systemic juvenile idiopathic arthritis.
- Use of biologics has steadily increased from 2008 to 2019 while glucocorticoid exposure has remained unchanged.
- Disease severity in the first 2 hospital days was associated with the decision to treat with biologics but was not associated with glucocorticoid exposure.
- There was significant treatment variation between US children's hospitals with higher utilization of biologics at high-volume hospitals and, conversely, higher utilization of glucocorticoids at low-volume hospitals.

setting and identify drivers of variation. Patients diagnosed with systemic JIA during inpatient hospitalization represent the highest acuity patient population, for which glucocorticoids and biologics are most commonly used. We leveraged encounter data from the Pediatric Health Information System (PHIS) to describe treatment variation among US children's hospitals, temporal trends, and patient- and hospital-level factors associated with first-line biologic and glucocorticoid use in a large inpatient multisite cohort of new-onset systemic JIA patients.

PATIENTS AND METHODS

This is a retrospective cohort study of children in the US hospitalized with new-onset systemic JIA. This study was reviewed and determined to be exempt by the Children's Hospital of Philadelphia (CHOP) Internal Review Board.

Data source. Subjects were obtained from the PHIS from January 1, 2008 to January 1, 2019. The PHIS is a comparative pediatric database that contains inpatient, emergency department, ambulatory surgery, and observation unit information from 52 not-for-profit, tertiary care pediatric hospitals. Data include demographic information, dates of service, discharge disposition, and daily inpatient billing data for medications, laboratory tests, imaging, procedures, clinical services, and supplies. Records can be linked longitudinally across admissions based on unique patient identifiers. Data are deidentified at the time of submission, and data quality is assured through a joint effort between the Children's Hospital Association and participating hospitals.

Study population. Children (<19 years) discharged from one of 52 PHIS hospitals between January 1, 2008 and March 31, 2019 were considered for inclusion if they had at least 1 hospitalization with an International Classification of Diseases, Ninth Revision (ICD-9) or ICD-10 discharge code for juvenile rheumatoid arthritis with systemic onset (714.30, M08.2x). The index admission was identified for patients with multiple admissions, which was defined as the first admission during the inclusion period without a prior discharge code of M08.2x or 714.30. Patients admitted to a hospital with ≤1 year of participation time in the PHIS prior to the index admission were excluded to ensure that a prior diagnosis of systemic JIA could be detected. Exclusion criteria included the following: 1) a primary discharge diagnosis of infection or malignancy; 2) patients who did not receive systemic JIA therapy to avoid including other diagnoses coded as 714.30, such as inflammatory bowel disease (IBD)–associated arthritis; 3) receipt of systemic JIA therapy other than scheduled nonsteroidal antiinflammatory drugs (NSAIDs) within the first 2 hospital days of admission to avoid inclusion of disease flare. The ICD-9 code for systemic JIA (714.30) is less specific than the ICD-10 code (M08.2x), necessitating additional exclusion criteria for patients discharged from January 1, 2008 to September 30, 2015 (last date prior to transition to the ICD-10 coding system): 1) discharge diagnostic codes for other rheumatologic conditions, uveitis, IBD; 2) absence of laboratory billing code for ferritin during the hospitalization. Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24417/abstract, includes a list of discharge ICD codes and clinical transaction classification (CTC) codes used in the exclusion criteria.

Medication exposure. Medication usage was determined using pharmacy billing data and CTC codes. Systemic JIA therapy was defined as methotrexate, glucocorticoids, anakinra, canakinumab, tocilizumab, or scheduled NSAIDs. Glucocorticoid exposure included oral or intravenous administration of dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and prednisone. Biologic exposure included anakinra, rilonacept, canakinumab, or tocilizumab. Scheduled use of NSAIDs was defined as a code for ibuprofen, naproxen, indomethacin, piroxicam, diclofenac, meloxicam, or celecoxib on ≥2 consecutive hospital days. Oral and subcutaneous methotrexate and intravenous and subcutaneous tocilizumab were pooled.

Validation of the study cohort. We validated the aforementioned process for identifying patients with new-onset systemic JIA at 2 PHIS participating centers, CHOP (ICD-9 and ICD-10 cohort) and Primary Children's Hospital (PCH) (ICD-9 cohort only). Patient charts were reviewed at these 2 centers and determined to be either true-positive or false-positive new-onset systemic JIA admissions using rheumatology provider diagnosis during the inpatient hospitalization as the reference standard. These values were then used to calculate the positive predictive values (PPV) separately for the ICD-9 and ICD-10 time periods.

Statistical analysis. All analyses were performed using data from the index admission. Standard descriptive statistics including range, mean and SD for normally distributed variables, or median and interquartile range (IQR) for nonnormally distributed

variables were used, as appropriate. Trends in treatment over time were assessed using an extension of the Wilcoxon's rank-sum test for trends and graphically displayed using simple linear regression. SD and coefficient of variation (CV) were used to describe variation in treatment between sites. In order to determine which clinical factors influenced the decision to treat with biologics and glucocorticoids, we fit a mixed-effects logistic regression model, accounting for within-hospital clustering by including a hospital-specific random effect. Separate models were fit for biologics and glucocorticoids. Other variables considered as fixed effects for each model included the year of admission, demographic information (age, sex, race, Medicaid insurance), hospital characteristics (region, mean systemic JIA volume per year, total annual patient volume, affiliated rheumatology fellowship), and disease-severity indicators within the first 2 hospital days prior to receipt of biologics or glucocorticoids. These disease-severity indicators included intensive care unit (ICU) status, supplemental oxygen, laboratory billing code for blood gas, and multiple complete blood counts in a single hospital day. Macrophage activation syndrome was not included in the model as the onset of macrophage activation syndrome during the hospitalization is unable to be determined in the PHIS database and may have occurred after treatment initiation. Stepwise selection was used to determine the final models. Likelihood ratio tests and Akaike's information criterion (AIC) and Bayesian information criterion (BIC) were used to confirm the final model selection. All analyses were performed using Stata, version 15.

RESULTS

A total of 3,729 patients age <19 years with an ICD-9 or ICD-10 code consistent with systemic JIA (714.30, M08.2x) discharged between January 1, 2008 and March 31, 2019 were identified in the PHIS database. After applying the exclusion criteria, a cohort of 534 patients was identified for analysis from 51 US children's hospitals distributed geographically across all 5 US regions (Figure 1). One PHIS hospital had no patients identified. The PPV of the study cohort identification process was 86.36% in the ICD-9 validation cohort (Table 1) and 100% in the ICD-10 validation cohort.

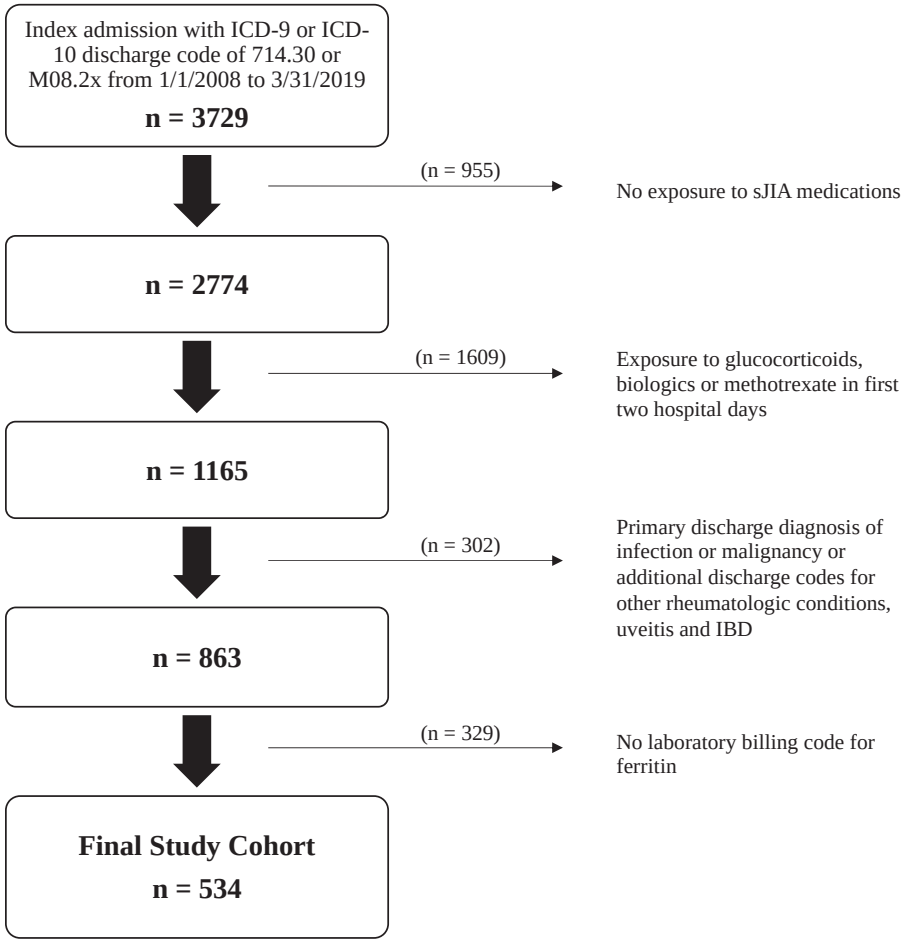

Figure 1. Inclusion and exclusion criteria and selection of the cohort. IBD = inflammatory bowel disease; ICD-9 = International Classification of Diseases, Ninth Revision; sJIA = systemic juvenile idiopathic arthritis.

Table 1. Positive predictive value (PPV) using systemic juvenile idiopathic arthritis (JIA) International Classification of Diseases, Ninth Revision (ICD-9) codes alone and in combination with additional exclusion criteria in Children's Hospital of Philadelphia (CHOP) and Primary Children's Hospital (PCH) validation cohorts*

Description	True-positives	False-positives	PPV, %
Step 1: ICD-9 code alone			
CHOP	16	120	11.76
PCH	12	127	8.63
Overall (n = 275)	28	247	10.18
Step 2a: Exclude admissions without CTC code for systemic JIA medications†			
CHOP	14	80	14.89
PCH	12	74	13.95
Overall (n = 180)	26	154	14.44
Step 2b: Same as step 2a, then exclude admissions with CTC code for glucocorticoids, biologics, or methotrexate in first 2 hospital days			
CHOP	11	26	29.73
PCH	8	23	25.81
Overall (n = 68)	19	49	27.94
Step 2c: Same as step 2b, then exclude admission with a primary discharge diagnosis of infection or malignancy and additional discharge codes for other rheumatologic conditions, uveitis, and IBD			
CHOP	11	22	33.33
PCH	8	12	40
Overall (n = 53)	19	34	35.85
Step 2d (final algorithm): Same as step 2c, then exclude admissions without a laboratory billing code for ferritin			
CHOP	11	1	91.67
PCH	8	2	80
Overall (n = 22)	19	3	86.36

* Values are the number unless indicated otherwise. Validation of ICD-9, Clinical Modification codes was done at 2 Pediatric Health Information System sites (CHOP and PCH). CTC = clinical transaction classification; IBD = inflammatory bowel disease.
† Interleukin-1 (IL-1) inhibitor, IL-6 inhibitor, glucocorticoids, methotrexate, or scheduled nonsteroidal antiinflammatory drugs.

Demographic information, clinical characteristics, and medication exposures of the cohort are shown in Table 2. The median age at diagnosis was 6 years (IQR 3–12). The percentage of patients receiving a biologic (26.0% IL-1 inhibitor, 3.7% IL-6 inhibitor) was 29.2%, and 57.9% received glucocorticoids. The median length of stay was 6 days (IQR 4.0–9.0), and the all-cause, 90-day readmission rate was 14%. The percentage of patients who required ICU level of care at some point during the hospitalization was 7.9%, and 11.8% of patients had a discharge diagnosis of macrophage activation syndrome, which was shown to be a reliable ICD-9 code in a prior PHIS study characterizing a cohort of JIA and systemic lupus erythematosus patients with macrophage activation syndrome (6). Biologic use significantly increased ($P < 0.001$), and methotrexate use significantly decreased ($P < 0.01$) from 2008 to 2019. Glucocorticoid use did not significantly change during this time period ($P = 0.70$) (Figure 2). There was significant variation between hospitals in the proportion of patients treated with biologics and glucocorticoids, with a median of 0.26 (IQR 0.11–0.40; CV 74.5%) and 0.61 (IQR 0.46–0.75; CV 39%), respectively.

The results of the multivariable mixed-effects logistic analysis to identify factors associated with biologic and glucocorticoid exposure at diagnosis are shown in Tables 3 and 4, respectively. Due to collinearity with annual hospital volume, average site systemic JIA volume per year was not included in the variable selection for multivariable analysis for biologic or glucocorticoid exposure. High annual hospital volume (odds ratio [OR] 6.68 [95% confidence interval (95% CI) 1.54–28.89]), ICU stay in the first 2 hospital days (OR 4.94 [95% CI 1.64–14.86]), and later discharge year were all significantly associated with biologic exposure. Annual hospital volume was the only variable found to be significantly associated with glucocorticoid exposure. This association was inversely proportional, with medium-high and high hospital volume associated with lower odds of glucocorticoid exposure (OR 0.15 [95% CI 0.05–0.44] and OR 0.30 [95% CI 0.11–0.79], respectively).

DISCUSSION

This study reports initial hospitalization characteristics and treatment approaches in 534 children diagnosed with systemic JIA across 52 geographically diverse US children's hospitals. The demographic information and clinical characteristics of our cohort, particularly age, sex, and diagnosis of macrophage activation

syndrome at disease onset, are comparable to those in previously published studies of systemic JIA cohorts (7–10). Our study highlights several important findings regarding treatment of patients with new-onset systemic JIA. First, use of biologics has steadily increased from 2008 to 2019 while glucocorticoid exposure has remained unchanged. Second, disease severity in the first 2 hospital days was associated with the decision to treat with biologics but was not associated with glucocorticoid exposure. Last, there was significant treatment variation between US children's hospitals with higher utilization of biologics at high-volume hospitals and, conversely, higher utilization of glucocorticoids at low-volume hospitals.

The first reports of successful use of IL-1 and IL-6 inhibition in systemic JIA were in 2005 (11–13). Randomized controlled trials over the next 7 years demonstrated the safety and efficacy of tocilizumab, anakinra, and canakinumab (2,3,14). In 2013, the American College of Rheumatology published an update to treatment recommendations for systemic JIA, recommending consideration of anakinra as initial therapy for patients with a physician global assessment of ≥5 as well as canakinumab or tocilizumab for patients with persistent disease activity, marking

Table 2. Patient characteristics*

Characteristic	Value (n = 534)
Demographic characteristics	
Age, median (IQR) years	6.0 (3.0–12.0)
Sex, male	281 (52.6)
Race	
White	354 (66.3)
Black	68 (12.7)
Asian	17 (3.2)
Other	95 (17.8)
Medicaid insurance	214 (40.1)
Hospital region	
Northeast	92 (17.2)
Southeast	90 (16.9)
Southwest	60 (11.2)
Midwest	156 (29.2)
West	136 (25.5)
Clinical features and medication exposures	
Length of stay, median (IQR) days	6.0 (4.0–9.0)
ICU level of care	42 (7.9)
Macrophage activation syndrome†	63 (11.8)
Glucocorticoids	309 (57.9)
Biologics‡	156 (29.2)
Anakinra	137 (25.7)
Canakinumab	11 (2.1)
Tocilizumab	20 (3.7)
Methotrexate	41 (7.7)
Scheduled NSAIDs	452 (84.6)
Readmission ≤90 days after discharge§	75 (14.0)

* Values are the number (%) unless indicated otherwise. ICU = intensive care unit; IQR = interquartile range; NSAIDs = nonsteroidal antiinflammatory drugs.
† Based on discharge International Classification of Diseases, Ninth Revision, Clinical Modification code. Diagnosis of macrophage activation syndrome may have occurred at any point during hospitalization.
‡ Not mutually exclusive. A total of 9 patients received both canakinumab and anakinra, and 3 patients received both anakinra and tocilizumab during hospitalization.
§ All-cause readmissions.

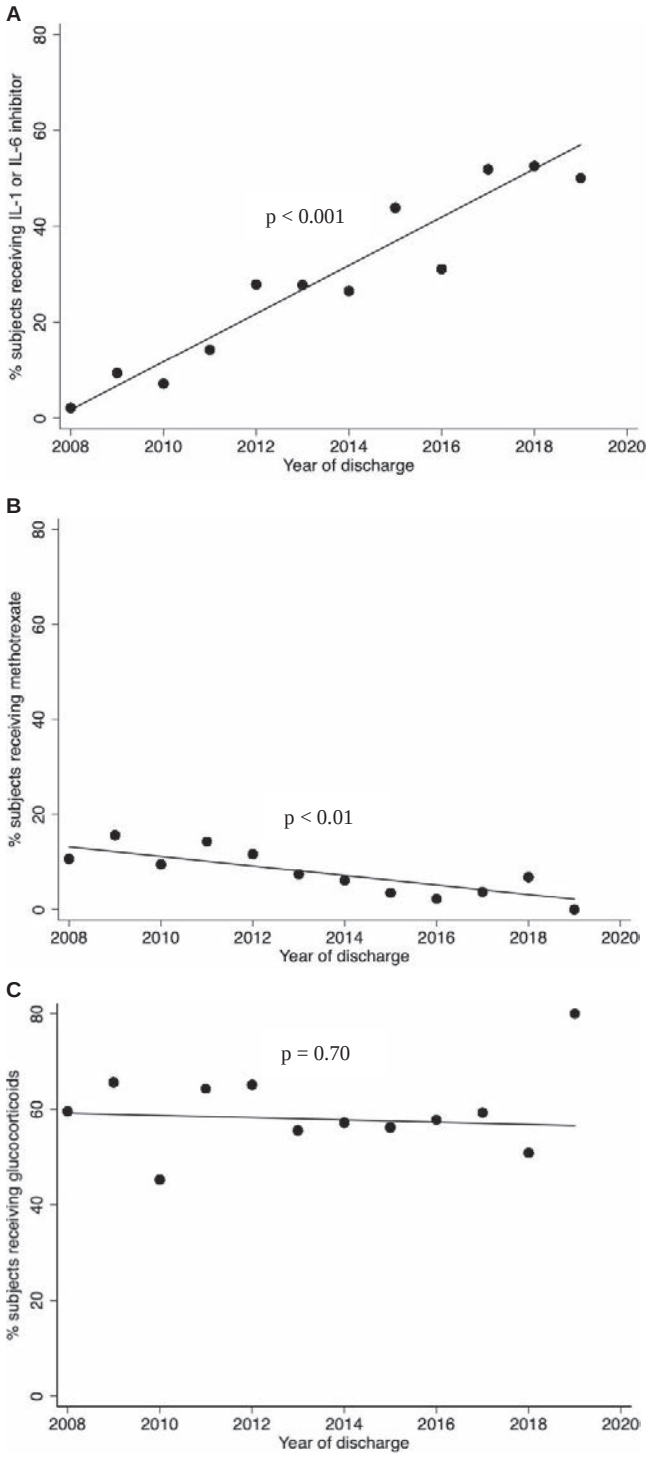

Figure 2. Change in the use of treatments for children hospitalized with new-onset systemic juvenile idiopathic arthritis from 2008 to 2019. *P* values for trends are shown. Each dot represents the raw percentage of patients in each year receiving biologics (interleukin-1 [IL-1] or IL-6 inhibitor) (**A**), methotrexate (**B**), and glucocorticoids (**C**). Lines indicate the best fit.

Table 3. Odds ratios (ORs) for association of biologic exposure with patient- and hospital-level factors*

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Patient-level factors		
Age, years	1.04 (0.70–1.54)	–
Female sex	0.88 (0.58–1.34)	0.69 (0.42–1.14)
Race		
White	Ref.	–
Black	1.48 (0.80–2.76)	–
Asian	1.88 (0.62–5.69)	–
Other	1.07 (0.60–1.94)	–
Medicaid insurance	1.43 (0.93–2.19)	–
Discharge year	†	†
Laboratory billing code for >1 complete blood count per day‡	2.59 (1.24–5.41)	2.35 (0.94–5.91)
Laboratory billing code for venous or arterial blood gas‡	2.84 (1.18–6.88)	–
ICU-level care‡	4.33 (1.70–11.06)	4.94 (1.64–14.86)
Hospital-level factors		
Systemic JIA volume§	1.47 (0.83–2.60)	–
Hospital inpatient admissions per year		
Low (≤12,000)	Ref.	Ref.
Medium to low (12,000–15,999)	1.35 (0.38–4.87)	1.64 (0.37–7.24)
Medium to high (16,000–21,000)	1.90 (0.57–6.39)	3.44 (0.82–14.41)
High (≥21,000)	3.59 (1.05–12.25)	6.68 (1.54–28.89)
Pediatric rheumatology fellowship	1.36 (0.63–2.97)	–
Region		
Northeast	Ref.	–
Southeast	1.18 (0.32–4.28)	–
Southwest	2.39 (0.58–9.81)	–
Midwest	1.14 (0.35–3.77)	–
West	1.03 (0.30–3.49)	–

* 95% CI = 95% confidence interval; ICU = intensive care unit; JIA = juvenile idiopathic arthritis; Ref. = reference group.
† Discharge year was a significant positive predictor of biologic exposure and included in the multivariable model (see Figure 2).
‡ Within the first 2 hospital days of admission.
§ Systemic JIA volume characterized as the mean number of systemic JIA patients per year at each site (not included in the multivariable model due to collinearity with annual hospital volume).

a major turning point in the treatment approach to systemic JIA (15). Our findings that treatment with biologics in new-onset systemic JIA has increased from 2008 to 2019 parallels the emerging evidence and treatment guideline changes over this time period. Conversely, we found that glucocorticoid use has remained unchanged over time despite prospective studies demonstrating positive clinical outcomes with biologic monotherapy (5,16). These temporal trends are consistent with previously published reports in other smaller observational cohort studies of patients with systemic JIA (7,8,10). Interestingly, we also found that decision to treat with glucocorticoids did not seem to be affected by markers of disease severity. Many providers may choose to treat new-onset systemic JIA with glucocorticoids as standard of care regardless of disease severity or anticipated response to alternative therapies such as biologics. While macrophage activation syndrome is an additional factor that contributes significantly to medication choice in new-onset systemic JIA, this was unable to be incorporated into the regression model due to unknown timing of macrophage activation syndrome onset during the hospitalization.

The finding of treatment variation between US children's hospitals in new-onset systemic JIA is not entirely unexpected. Provider surveys informing the creation of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus treatment plans (CTPs) as well as the initial CTP utilization highlighted significant interprovider and intersite variability (17). The association of hospital volume with glucocorticoid and biologic exposure, however, is a novel finding. Even after correcting for discharge year and markers of disease severity prior to treatment administration, hospitals with higher patient volume were more likely to prescribe biologics for new-onset systemic JIA patients and less likely to prescribe glucocorticoids. While there is the potential for residual confounding by indication that our models did not adjust for, we would have anticipated that high-volume hospitals cared for sicker patients. Therefore, if residual confounding by indication persisted, this would have artificially increased the reported likelihood of glucocorticoid exposure at high-volume hospitals. Additionally, high-volume hospitals did not have a significantly different rate of discharge ICD code for macrophage activation syndrome compared to low-volume hospitals, suggesting that the case mix

Table 4. Odds ratios (ORs) for association of glucocorticoid exposure with patient- and hospital-level factors*

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Patient-level factors		
Age, years	1.02 (0.99–1.06)	–
Female sex	1.02 (0.70–1.49)	–
Race		
White	Ref.	–
Black	0.92 (0.51–1.65)	–
Asian	0.93 (0.31–2.76)	–
Other	1.15 (0.68–1.95)	–
Medicaid insurance	0.99 (0.67–1.47)	–
Discharge year	†	–
Laboratory billing code for >1 complete blood count per day‡	1.42 (0.68–2.94)	–
Laboratory billing code for venous or arterial blood gas‡	2.07 (0.84–5.09)	–
ICU-level care‡	1.66 (0.65–4.24)	–
Hospital-level factors		
Systemic JIA volume§	0.78 (0.49–1.24)	–
Hospital inpatient admissions per year		
Low (≤12,000)	Ref.	Ref.
Medium to low (12,000–15,999)	0.68 (0.24–1.94)	0.47 (0.16–1.37)
Medium to high (16,000–21,000)	0.30 (0.11–0.81)	0.15 (0.05–0.44)
High (≥21,000)	0.35 (0.13–0.95)	0.30 (0.11–0.79)
Pediatric rheumatology fellowship	0.72 (0.38–1.35)	–
Region		
Northeast	Ref.	–
Southeast	0.59 (0.21–1.68)	0.75 (0.28–2.06)
Southwest	1.18 (0.36–3.85)	1.35 (0.46–3.92)
Midwest	0.97 (0.37–2.52)	1.24 (0.46–3.36)
West	1.27 (0.47–3.39)	3.11 (0.98–9.89)

* 95% CI = 95% confidence interval; ICU = intensive care unit; JIA = juvenile idiopathic arthritis; Ref. = reference group.
† Discharge year was not a significant predictor of glucocorticoid exposure and not included in the multivariable model (see Figure 2).
‡ Within the first 2 hospital days of admission.
§ Systemic JIA volume characterized as the mean number of systemic JIA patients per year at each site (not included in the multivariable model due to collinearity with annual hospital volume).

among hospitals is comparable (P = 0.37). We hypothesize that physicians at higher volume hospitals may have more experience and comfort with using biologic medications. These sites may also have easier access to biologics through the inpatient pharmacy, whereas smaller sites may rely more on outpatient pharmacies and patient assistance programs, which would not have been captured in the PHIS database. Further studies are needed to describe the specific causes of treatment variation and to identify potential barriers to first-line biologic use in new-onset systemic JIA.

There were several limitations to our study. First, it is important to note that we were unable to evaluate continuation or dose of glucocorticoid therapy after hospital discharge. The duration of outpatient glucocorticoid treatment may be decreasing over time with improving clinical outcomes in systemic JIA, which was shown in a recently published single-site cohort study of new-onset systemic JIA patients diagnosed between 1995 and 2015 (10). Second, there was the potential for misclassification of the cohort, which is an inherent risk in epidemiologic studies utilizing administrative claims databases in which identification of patients is based on diagnostic codes. We attempted to overcome this misclassification by incorporating additional criteria for cohort inclusion. This process resulted in acceptable PPVs in the ICD-9 and ICD-10 cohorts, suggesting that most of the patients included in the cohort were truly new-onset systemic JIA patients. It is important to note that we were unable to assess the sensitivity of our patient identification process. The restrictive inclusion and exclusion criteria may have led to omission of a small subset of patients with new-onset disease, particularly those in whom the diagnosis was certain on admission and who received treatment within the first 2 hospital days. However, this approach was thought to be necessary to avoid including patients admitted with systemic JIA flares in the final cohort. Third, there may have been confounding by center in which treatment choice strongly clustered with individual site. We incorporated analytic techniques to address this by including site as a random effect in our mixed effects logistic regression model, but residual confounding by center may have persisted. Fourth, due to small numbers of patients receiving IL-6 inhibition at diagnosis (n = 20), comparisons were unable to be made between IL-1 and IL-6 inhibition, and these 2 patient groups were analyzed together in the biologic exposure group. Finally, this study was limited to children

who required hospitalization at pediatric centers for diagnosis and initiation of treatment for systemic JIA, so our results may not be generalizable to all children with systemic JIA or patients diagnosed in the outpatient setting. However, children who require hospitalization represent the population with new-onset systemic JIA with the highest acuity and for whom the risk of morbidity and mortality is the highest. This patient population is the most likely to require first-line treatment with therapies such as biologics and glucocorticoids and thus would benefit the most from movement toward more standardized care.

As increasing evidence emerges demonstrating improved outcomes with first-line treatment with biologics, it is critical to identify barriers to implementation of evidence-based care. There remains significant treatment variation across hospitals with a large proportion of children not receiving biologics and a persistence of high rates of glucocorticoid exposure over time. These results point to the need for more robust data regarding the comparative efficacy of treatment strategies at diagnosis in the highest acuity, hospitalized, systemic JIA population followed by improved treatment standardization.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Weiss had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Peterson, Xiao, Fisher, Weiss.
Acquisition of data. James, Katcoff.
Analysis and interpretation of data. Peterson, Xiao, Fisher, Weiss.

REFERENCES

1. Beukelman T. Treatment advances in systemic juvenile idiopathic arthritis. F1000Prime Rep 2014;6:21.
2. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2396–406.
3. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2385–95.
4. DeWitt EM, Kimura Y, Beukelman T, Nigrovic PA, Onel K, Prahalad S. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2012;64:1001–10.
5. Ter Haar NM, van Diikhuizen EH, Swart JF, van Roven-Kerkhof A, El Idrissi A, Leek AP, et al. Treatment to target using recombinant interleukin-1 receptor antagonist as first-line monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five-year follow-up study. Arthritis Rheumatol 2019;71:1163–73.
6. Bennett TD, Fluchel M, Hersh AO, Hayward KN, Hersh AL, Brogan TV, et al. Macrophage activation syndrome in children with systemic lupus erythematosus and children with juvenile idiopathic arthritis. Arthritis Rheum 2012;64:4135–42.
7. Janow G, Schanberg LE, Setoguchi S, Hasselblad V, Mellins ED, Schneider R, et al. The Systemic Juvenile Idiopathic Arthritis cohort of the Childhood Arthritis and Rheumatology Research Alliance Registry: 2010–2013. J Rheumatol 2016;43:1755–62.
8. Klotsche J, Raab A, Niewerth M, Sengler C, Ganser G, Kallinich T, et al. Outcome and trends in treatment of systemic juvenile idiopathic arthritis in the German National Pediatric Rheumatologic Database, 2000–2013. Arthritis Rheumatol 2016;68:3023–34.
9. Sawhney S, Woo P, Murray K. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child 2001;85:421–6.
10. Baris H, Anderson E, Sozeri B, Dedeoglu F. Impact of biologics on disease course in systemic onset juvenile idiopathic arthritis. Clin Rheumatol 2018;37:3263–73.
11. Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. J Exp Med 2005;201:1479–86.
12. Woo P, Wilkinson N, Prieur A, Southwood T, Leone V, Livermore P, et al. Open label phase II trial of single, ascending doses of MRA in Caucasian children with severe systemic juvenile idiopathic arthritis: proof of principle of the efficacy of IL-6 receptor blockade in this type of arthritis and demonstration of prolonged clinical improvement. Arthritis Res Ther 2005;7:R1281–8.
13. Yokota S, Miyamae T, Imagawa T, Iwata N, Katakura S, Mori M, et al. Therapeutic efficacy of humanized recombinant anti–interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 2005;52:818–25.
14. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet 2008;371:998–1006.
15. Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis. Arthritis Rheum 2013;65:2499–512.
16. Pardeo M, Bracaglia C, Tulone A, Insalaco A, Marucci G, Nicolai R. Op0057 Early treatment with anakinra in systemic juvenile idiopathic arthritis. Ann Rheum Dis 2019;78:100.
17. Kimura Y, Grevich S, Beukelman T, Morgan E, Nigrovic PA, Mieszkalski K, et al. Pilot study comparing the Childhood Arthritis & Rheumatology Research Alliance (CARRA) systemic juvenile idiopathic arthritis consensus treatment plans. Pediatr Rheumatol Online J 2017;15:23.

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Determinants of Discordance Between Criteria for Inactive Disease and Low Disease Activity in Juvenile Idiopathic Arthritis

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Objective. To assess concordance among criteria for inactive disease (ID) and low disease activity (LDA) in juvenile idiopathic arthritis (JIA) and to seek factors driving discordance.

Methods. The frequency of fulfillment of existing criteria was evaluated in information on 10,186 patients extracted from 3 cross-sectional data sets. Patients were divided up according to the functional phenotypes of oligoarthritis and polyarthritis. Concordance between criteria was examined using weighted Venn diagrams. The role of each individual component in explaining discordance between criteria was assessed by calculating the absolute number and percentage of instances in which the component was responsible for discrepancy between definitions.

Results. Criteria for ID were met by 28.6–41.1% of patients with oligoarthritis and by 24.0–33.4% of patients with polyarthritis. Criteria for LDA were met by 44.8–62.4% of patients with oligoarthritis and by 44.6–50.4% of patients with polyarthritis. There was a 57.9–62.3% overlap between criteria for ID and a 67.9–85% overlap between criteria for LDA. Parent and physician global assessments and acute-phase reactants were responsible for the majority of instances of discordance among criteria for ID (8.7–15.5%, 10.0–12.3%, and 10.8–17.3%, respectively).

Conclusion. We found fair concordance between criteria for ID and LDA in JIA, with the main drivers of discordance for ID being physician and parent global assessments and acute-phase reactants. This observation highlights the need for further studies aimed to evaluate the impact of subjective physician and parent perception of disease remission and of laboratory measures of inflammatory activity on the definition of ID.

INTRODUCTION

Over the past 2 decades, there has been a remarkable advance in the management of juvenile idiopathic arthritis (JIA), which has made remission an achievable goal for the vast majority of patients (1). The recent recommendations for the treat-to-target strategy in JIA have set inactive disease (ID) as the primary target for treatment, with the alternative target of low (or minimal) disease

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- Although several definitions for inactive disease (ID) and low disease activity (LDA) in juvenile idiopathic arthritis (JIA) are available, it is still unclear which criteria are best suited.
- This study examined the concordance between existing criteria for ID and LDA in JIA and sought for determinants of discordance.
- Fair overlap between criteria was observed. The physician and parent global assessments and acute-phase reactants were the main determinants of discordance between criteria for ID.

activity (LDA), particularly in patients with long-standing disease (2). Thus, modern therapeutic management of children with JIA requires the regular application of well-established and reliable criteria for ID and LDA.

The definitions of ID and LDA currently used in JIA have been developed following 2 different approaches. The first was based on the combination of multiple criteria, all of which should be met, and includes the preliminary criteria for clinical remission (2004 ID criteria) (3), the American College of Rheumatology provisional criteria for defining clinical ID (2011 ID criteria) (4), and the preliminary definition of minimal disease activity in oligoarthritis and polyarthritis (2008 LDA criteria) (5). The second group of definitions has been obtained by calculating the cutoff in the Juvenile Arthritis Disease Activity Score (JADAS) (6) and in the clinical (i.e., 3-item) JADAS (cJADAS) (7) that corresponds to the states of ID and LDA (the JADAS or cJADAS ID criteria and JADAS or cJADAS LDA criteria, respectively). For the sake of simplicity, the acronym ID will be used collectively for the terms "inactive disease," "clinical remission," and "clinical inactive disease."

There are several differences between the above definitions, the chief of which regards the inclusion of the parent/patient global assessment of the child's well-being. This measure is not incorporated in the 2004 and 2011 ID criteria, which are only based on physician-reported measures and acute-phase reactant (APR), but is comprised in the JADAS and cJADAS criteria. The parent's/patient's global assessment is part of the 2008 LDA criteria for polyarthritis but not of those for oligoarthritis. Other diversities include assessment of uveitis activity, requested only by the 2004 and 2011 ID criteria, estimation of morning stiffness (MS) duration, required only by the 2011 ID criteria, and count of swollen joints, necessary only to assess the 2008 LDA criteria. In addition, determination of APR is not included in the cJADAS and the 2008 LDA criteria. However, it is still unclear which criteria are more advantageous.

Shoop-Worral et al (8) recently found poor overlap (only 44% of patients) between the 2004 ID criteria and the JADAS ID criteria, suggesting that these criteria, which are intended to capture the same disease state, identify diverse groups of children. Based on this finding, the concern was raised that use of different criteria to define ID and LDA in clinical practice could potentially lead to overtreatment or undertreatment. The most likely explanation for the scarce concordance was the inflating effect of the parent's global assessment of the child's well-being, which is included in the JADAS and not in the 2004 ID criteria. Another source of discordance was the tendency of some clinicians not to mark the visual analog scale (VAS) for physician global assessment of disease activity (PhGA) at exactly 0, even on resolution of active disease. However, thus far, the role of the other components in explaining discordance and the concordance of the JADAS ID criteria with that of the 2011 ID criteria has not been studied. Against this background, the current study was aimed to evaluate the degree of concordance among all existing criteria for ID and LDA in JIA and to seek determinants of discordance.

PATIENTS AND METHODS

Study design and patient selection. The following 3 cross-sectional data sets, comprising patients meeting the International League of Associations for Rheumatology (ILAR) criteria for JIA (9), were used for the study analyses. The first was composed of 669 patients included in a study performed at the Gaslini Institute of Genoa, Italy and aimed to validate the parent and child versions of a multinational questionnaire (Gaslini data set) (10). The second included 422 patients recruited in a survey of etanercept therapy at Italian pediatric rheumatology centers (EtICA data set) (11). The third comprised 9,081 patients enrolled in a multinational study of the epidemiology, treatment, and outcome of JIA (EPOCA data set) (12). For simplicity and to facilitate the application of the ID and LDA criteria, patients were grouped according to the functional phenotypes of oligoarthritis and polyarthritis. Oligoarthritis included persistent oligoarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. Polyarthritis included extended oligoarthritis, rheumatoid factor (RF)-positive and RF-negative polyarthritis, and systemic arthritis. Ethics committee approval was previously obtained for all 3 studies.

Criteria for ID and LDA. The following definitions of ID and LDA were assessed: 1) The 2004 ID criteria (3), which require the simultaneous presence of a) no active joints, b) absence of systemic symptoms attributable to JIA, c) absence of active uveitis, d) normal APR (if both erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] level are tested, both should be normal), and e) PhGA indicating no disease activity. 2) The 2011 ID criteria (4), which updated the 2004 version by specifying the definition of inactive uveitis, acknowledging that APR can be elevated for reasons unrelated to JIA, and adding, as a sixth criterion, the presence of MS lasting ≤15 minutes. 3) The JADAS in 10 joints (JADAS-10) criteria for ID and LDA. Briefly, the JADAS-10 is composed of the following 4 variables: a) the PhGA; b) the parent

global assessment; c) a 10-joint count of active joints (13); d) the ESR or CRP level, each normalized on a 0–10 scale, as reported (14,15). For the calculation of the JADAS-10, if both the ESR and CRP level were tested, their normalized value was averaged. The JADAS-10 ranges from 0 to 40 (0 = no activity; 40 = maximum activity), and a score of ≤1 indicates ID in both oligoarthritis and polyarthritis, whereas scores comprised between 1.1 and 2 and between 1.1 and 3.8 for oligoarthritis and polyarthritis, respectively, indicate LDA (6). 4) The cJADAS-10 criteria for ID and LDA. The cJADAS-10 is made up of the same elements as the JADAS-10, except for the lack of a variable for APR. The cJADAS-10 ranges from 0 to 30 (0 = no activity; 30 = maximum activity), and a score of ≤1 indicates ID in both oligoarthritis and polyarthritis, whereas scores comprised between 1.1 and 1.5 and between 1.1 and 2.5 for oligoarthritis and polyarthritis, respectively, indicate LDA (7). 5) The 2008 LDA criteria (5). By these criteria, LDA is established in the presence of a PhGA of ≤2.5 and a swollen joint count of 0 in oligoarthritis, and in the presence of a PhGA of ≤3.4, a parent global assessment of ≤2.1, and a swollen joint count of ≤1 in polyarthritis. In children with systemic arthritis, the JADAS-10 and cJADAS-10 criteria as well as the 2008 LDA criteria require the absence of systemic manifestations. For the assessment of all criteria, the PhGA and the parent global assessment were rated using a 21-circle VAS (0 = best; 10 = worse) (16). The composition of the criteria for ID and LDA used in this study is shown in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24415/abstract.

Statistical analyses. Descriptive statistics are reported as the median and interquartile range (IQR) for continuous variables and as absolute frequency and percentage for categorical variables. Comparisons of demographic and clinical features among the 3 data sets were conducted using a chi-square test and Kruskal-Wallis test, as appropriate. All definitions of ID and LDA were assessed on extracted data items at the time of the study visit. All visits in which the patient met at least 1 of the definitions of ID or LDA were evaluated. The percentage of patients who met each definition was then calculated, and the concordance between definitions was examined by means of a weighted Venn diagram. Agreement among criteria was assessed by means of Fleiss' kappa and was interpreted as follows: <0.20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, optimal. Analyses were conducted using R software, version 3.0.1, "irr" package. The impact of the individual components of each set of criteria in explaining discordance was

Table 1. Demographic and clinical characteristics of patients included in the 3 study data sets*

Characteristic	Gaslini (n = 669)	EtICA (n = 422)	EPOCA (n = 9,081)	*P*
Female	528 (78.9)	335 (79.4)	6,030 (66.4)	<0.001
Age at disease onset, median (IQR) years	2.9 (1.8–6.0)	3.5 (1.8–7.3)	5.5 (2.5–9.7)	<0.001
Disease duration, median (IQR) years	10.1 (6.1–13.9)	7.1 (4.2–11.0)	11.6 (7.6–14.8)	<0.001
ILAR category				<0.001
Systemic arthritis	46 (6.9)	21 (5.0)	970 (10.7)	
RF-negative polyarthritis	128 (19.1)	138 (32.7)	2,141 (23.6)	
RF-positive polyarthritis	10 (1.5)	16 (3.8)	382 (4.2)	
Persistent oligoarthritis	298 (44.5)	60 (14.2)	2,838 (31.3)	
Extended oligoarthritis	139 (20.8)	147 (34.8)	971 (10.7)	
Psoriatic arthritis	15 (2.2)	16 (3.8)	959 (10.6)	
Enthesitis-related arthritis	13 (1.9)	21 (5.0)	309 (3.4)	
Undifferentiated arthritis	20 (3.1)	3 (0.7)	511 (5.6)	
Functional phenotype				<0.001
Oligoarthritis	342 (51.1)	100 (23.7)	4,456 (49.1)	
Polyarthritis	327 (48.9)	322 (76.3)	4,625 (50.9)	
ESR, median (IQR)	13 (8–23)	10 (5–16)	10 (5–20)	<0.001
CRP, median (IQR)	0.5 (0.5–0.5)	0.45 (0.27–0.45)	1.0 (0.28–4.0)	<0.001
Present treatment				
Intraarticular glucocorticoids	NA	98 (23.2)	48 (0.5)	–
Methotrexate	209 (31.2)	311 (73.7)	4,316 (47.5)	<0.001
Other synthetic DMARDs	11 (1.6)	17 (4.0)	731 (8.1)	<0.001
Biologic DMARDs	100 (15.0)	422 (100.0)	2,314 (25.5)	<0.001
Systemic glucocorticoids	36 (5.4)	93 (22.0)	1,257 (13.8)	<0.001
No therapy	278 (41.6)	0.0 (0.0)	1,655 (18.2)	<0.001

* Values are the number (%) unless indicated otherwise. CRP = C-reactive protein; DMARDs = disease-modifying antirheumatic drugs; EPOCA = Epidemiology, Treatment, and Outcome of Childhood Arthritis Throughout the World (data set); ESR = erythrocyte sedimentation rate; EtICA = Italian pediatric rheumatology centers (data set); ILAR = International League of Associations for Rheumatology; IQR = interquartile range; NA = not available; RF = rheumatoid factor.

assessed by calculating the absolute number and percentage of instances in which a particular component was responsible for the discordance between definitions. Due to the large number of comparisons, the differences were only interpreted qualitatively. No imputation for missing data was performed, and only patients/visits that included all items necessary to assess each definition were retained. Comparisons between pairs of definitions was made only on patients/visits that had all items necessary to assess both definitions available.

RESULTS

Patient population. A total of 10,172 patients, extracted from the Gaslini (n = 669), EtICA (n = 422), and EPOCA (n = 9,081) data sets, were included in the analyses. The demographic and clinical characteristics of the study samples are presented in Table 1. As compared to the Gaslini and EtICA data sets, the EPOCA data set was characterized by lesser female predominance, older age at disease onset, and a higher proportion of systemic and psoriatic arthritis. The Gaslini sample included a higher percentage of patients with persistent oligoarthritis and a lower percentage of patients receiving pharmacologic treatments. In comparison to the Gaslini and EPOCA data sets, the EtICA sample had shorter disease duration and higher frequency of patients with polyarticular disease course and receiving methotrexate and systemic glucocorticoids.

Frequency of fulfillment of the criteria for ID and LDA. The frequency of fulfillment of the definitions of ID and LDA in patients with oligoarthritis and polyarthritis is shown in Supplementary Tables 2 and 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24415/abstract. As expected, patients in the EtICA data set, all of whom were receiving etanercept, had a higher frequency of ID and LDA by all criteria than the Gaslini and EPOCA samples, which were composed of unselected patients followed in routine care. The frequency of fulfillment of criteria for ID was higher among Gaslini patients than in the EPOCA cohort. The overall frequency of ID and LDA was higher in patients with oligoarthritis than in those with polyarthritis, with the exception of the JADAS and cJADAS criteria for LDA, the fulfillment of which was comparable across disease phenotypes.

Because it was felt that the different composition of the data sets could enhance the representativeness of the patient population, they were combined in the subsequent analyses. In the entire sample, the 2004, 2011, and the JADAS-10 criteria for ID were met with comparable frequency, whereas the 2011 ID criteria were slightly more stringent. Substantial agreement was observed among definitions of ID for both oligoarthritis ($\kappa = 0.722$, $\zeta = 107$, $P = 0.000$) and polyarthritis ($\kappa = 0.737$, $\zeta = 117$, $P = 0.000$). Among criteria for LDA, agreement was good for oligoarthritis ($\kappa = 0.689$, $\zeta = 70.9$, $P = 0.000$) and optimal ($\kappa = 0.856$, $\zeta = 96.2$, $P = 0$) for polyarthritis.

Analysis of concordance among criteria. The degree of concordance among criteria was assessed by drawing Venn diagrams, which are shown in Figures 1 and 2, and in Supplementary Figures 1 and 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24415/abstract. Concordance was evaluated by comparing as pairs the

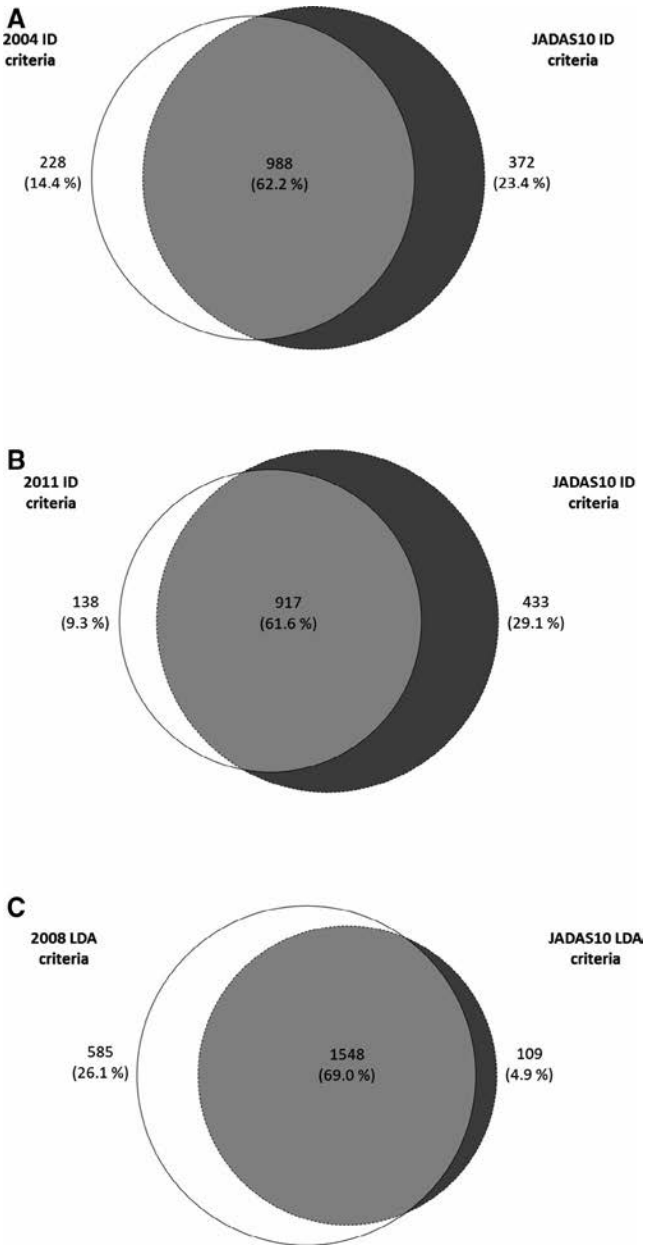

Figure 1. Percentage of patient overlap between criteria for inactive disease (ID) and criteria for low disease activity (LDA) in patients with oligoarthritis in the 3 study data sets combined. **A**, 2004 criteria for ID versus Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10) criteria for ID. **B**, 2011 criteria for ID versus JADAS-10 criteria for ID. **C**, 2008 criteria for LDA versus JADAS-10 criteria for LDA. For each figure, percentages are out of all children who satisfied at least 1 of the criteria displayed.

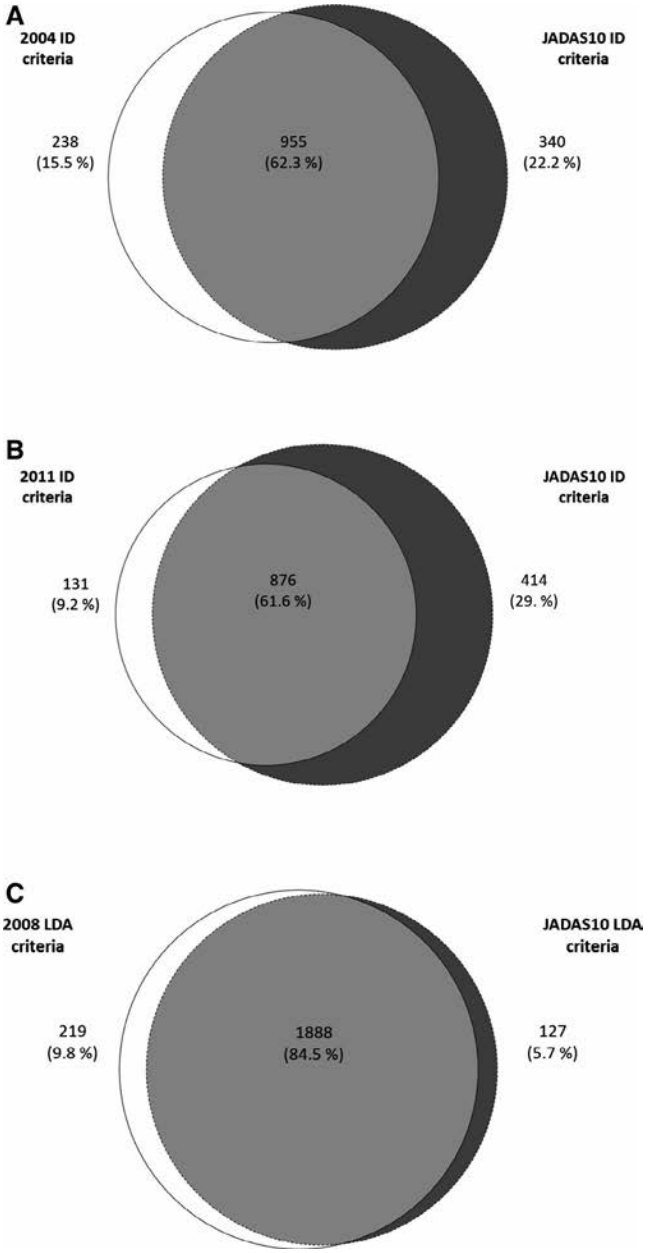

Figure 2. Percentage of patient overlap between criteria for inactive disease (ID) and criteria for low disease activity (LDA) in patients with polyarthritis in the 3 study data sets combined. **A**, 2004 criteria for ID versus Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10) criteria for ID. **B**, 2011 criteria for ID versus JADAS-10 criteria for ID. **C**, 2008 criteria for LDA versus JADAS-10 criteria for LDA. For each figure, percentages are out of all children who satisfied at least 1 of the criteria displayed.

definitions based on multiple criteria with those centered on the JADAS-10 and cJADAS-10.

In patients with oligoarthritis, there was a 58.0% to 69.0% overlap between criteria. Both the 2004 and 2011 ID criteria were consistently met by fewer patients than the JADAS-10 and cJADAS-10 ID criteria. Conversely, the 2008 LDA criteria were met by a higher proportion of patients than both the JADAS-10 and cJADAS-10 LDA criteria.

The trend was similar in patients with polyarthritis (57.9–85% overlap). Furthermore, the overlap between the 2008 LDA criteria and the JADAS-10 and cJADAS-10 LDA criteria was higher than in oligoarthritis.

In general, the degree of overlap with the JADAS and cJADAS ID criteria was similar for the 2011 and 2004 ID criteria. The frequency and direction of discordance between definitions were similar across all data sets, with the exception of a higher frequency of fulfillment of the JADAS-10 and cJADAS-10 ID criteria without meeting the 2004 and 2011 ID criteria in the EPOCA data set, particularly in polyarthritis (see Supplementary Tables 4, 5, and 6, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24415/abstract).

Factors driving discordance among criteria. The impact of individual components in driving discordance between criteria for ID and LDA is summarized for oligoarthritis in Table 2 and Supplementary Tables 7 and 8, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24415/abstract, and for polyarthritis in Tables 3 and 4 and Supplementary Table 9, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24415/abstract.

The parent global assessment, which is included in the JADAS-10 and cJADAS-10 and not in the 2004 and 2011 ID criteria, was the leading factor explaining discordance among patients meeting the 2004 and 2011 ID criteria and not fulfilling the JADAS-10 and cJADAS-10 ID criteria. This finding means that in 8.7–15.5% of instances the parent provided a VAS score of >1 when the PhGA was 0 and APRs were normal.

Conversely, the PhGA was involved more frequently (10.0–12.3% of instances) in discordance between fulfillment of the JADAS-10 and cJADAS-10 criteria and not fulfillment of the 2004 and 2011 ID criteria. This observation implies that the physicians did not always mark a score of 0 on the PhGA VAS when the patient had no active joints. Note that the active joint count accounted for only 0.7–1.9% of discordant evaluations. Duration of morning stiffness >15 minutes was responsible for 6.7–7.7% of discrepancies between fulfilled JADAS and cJADAS ID criteria and unmet 2004 and 2011 Wallace criteria.

APRs played a major role in determining discordance (10.8–17.3% of instances) when the JADAS and cJADAS ID criteria were met and the 2004 and 2011 ID criteria were not met. Their impact was much less relevant in the discordance between fulfillment of the 2008 LDA criteria and nonfulfillment of the JADAS-10 and cJADAS-10 definitions of LDA, where the PhGA and parent global assessment explained the majority of instances of discordance. Disparities were much less common among patients who met the JADAS-10 and cJADAS-10 definitions of LDA and

Table 2. Factors driving discordance between the 2004 and 2011 criteria for inactive disease (ID) and the Juvenile Disease Activity Score in 10 joints (JADAS-10) criteria for ID in oligoarthritis*

	2004 ID criteria met, JADAS-10 ID criteria not met	2004 ID criteria not met, JADAS-10 ID criteria met	2011 ID criteria met, JADAS-10 ID criteria not met	2011 ID criteria not met, JADAS-10 ID criteria met
No. of positive/total observations (%)†	228/1,588 (14.4)	372/1,588 (23.4)	138/1,488 (9.3)	433/1,488 (29.1)
Determinants of discordance				
Parent global assessment	228 (14.4)	–	138 (9.3)	–
Acute-phase reactants	–	172 (10.8)	–	172 (11.6)
PhGA	–	172 (10.8)	–	171 (11.5)
Active joint count	–	25 (1.6)	–	25 (1.7)
Active uveitis	–	27 (1.7)	–	27 (1.8)
Morning stiffness	–	–	–	99 (6.7)

* Values are the number (%) unless indicated otherwise. The 2004 criteria for ID are not met when either the physician global assessment of disease activity (PhGA) or the active joint count are >0, acute-phase reactants are abnormal, or the patient has active uveitis. The 2011 criteria for ID are not met when, in addition to any of the above, morning stiffness duration is >15 minutes. The JADAS-10 criteria for ID are not met when the sum of the scores of the 4 JADAS-10 components (PhGA, parent global assessment, active joint count, and acute-phase reactant) is >1.
† Observations with discordance/observations with paired assessment of both criteria.

not the 2008 LDA criteria. These findings likely depend on the lesser stringency of the latter criteria.

DISCUSSION

We investigated the frequency of achievement of the states of ID and LDA by all existing criteria in 10,172 children with JIA. The study population was extracted from 3 cross-sectional data sets comprising a national and a multinational sample of patients followed in routine clinical care and a cohort of patients treated with etanercept. Altogether, these patients are likely representative of the entire spectrum of children with JIA seen in pediatric rheumatology centers worldwide.

In the entire sample, we found that the 2004, 2011, and the JADAS-10 ID criteria were met with comparable frequency, whereas the 2011 ID criteria tended to be more stringent. Furthermore, the overlap between the 2004 and JADAS-10 ID criteria and between the 2011 and JADAS-10 ID criteria was comparable, with approximately two-thirds of patients meeting both pairs of criteria in both oligoarthritis and polyarthritis samples. Overlap between LDA criteria was higher in patients with polyarthritis.

Our results differ from those reported by Shoop-Worral et al (8), who found that the proportion of children with ID captured by the 2004 ID criteria was lower than that detected by the JADAS-10 ID criteria (25% versus 38%). In addition, the overlap between the 2 sets of criteria (44%) was poorer than that seen in our study. These disparities may depend on differences in study design, patient characteristics, and completeness of available data.

Shoop-Worral et al (8) stated that the most likely explanation for the scarce concordance between definitions was the role of the

Table 3. Factors driving discordance between the 2004 and 2011 criteria for inactive disease (ID) and the Juvenile Disease Activity Score in 10 joints (JADAS-10) criteria for ID in polyarthritis*

	2004 ID criteria met, JADAS-10 ID criteria not met	2004 ID criteria not met, JADAS-10 ID criteria met	2011 ID criteria met, JADAS-10 ID criteria not met	2011 ID criteria not met, JADAS-10 ID criteria met
No. of positive/total observations (%)†	238/1,533 (15.5)	340/1,533 (22.2)	131/1,421 (9.2)	414/1,421 (29.1)
Determinants of discordance				
Parent global assessment	238 (15.5)	–	131 (9.2)	–
Acute-phase reactants	–	169 (11.0)	–	169 (11.9)
PhGA	–	153 (10.0)	–	153 (10.8)
Active joint count	–	11 (0.7)	–	11 (0.8)
Active uveitis	–	23 (1.5)	–	23 (1.6)
Morning stiffness	–	–	–	107 (7.5)
Active systemic manifestations	–	6 (0.4)	–	6 (0.4)

* Values are the number (%) unless indicated otherwise. The 2004 criteria for ID are not met when either the physician global assessment of disease activity (PhGA) or the active joint count are >0, acute-phase reactants are abnormal, or the patient has active uveitis or active systemic manifestations. The 2011 criteria for ID are not met when, in addition to any the above, morning stiffness duration is >15 minutes. The JADAS-10 criteria for ID are not met when the sum of the scores of the 4 JADAS-10 components (PhGA, parent global assessment, active joint count, and acute-phase reactant) is >1.
† Observations with discordance/observations with paired assessment of both criteria.

Table 4. Factors driving discordance between the 2008 criteria for low disease activity (LDA) and the Juvenile Disease Activity Score in 10 joints (JADAS-10) and clinical JADAS-10 (cJADAS-10) criteria for LDA in polyarthritis*

	2008 LDA criteria met, JADAS-10 LDA criteria not met	2008 LDA criteria not met, JADAS-10 LDA criteria met	2008 LDA criteria met, cJADAS-10 LDA criteria not met	2008 LDA criteria not met, cJADAS-10 LDA criteria met
No. of positive/total observations (%)†	219/2,234 (9.8)	127/2,234 (5.7)	345/2,620 (13.2)	49/2,620 (1.9)
Determinants of discordance				
PhGA	204 (9.1)	1 (0)	343 (13.1)	–
Swollen joint count	–	41 (1.8)	–	22 (0.8)
Parent global assessment	175 (7.8)	85 (3.8)	278 (10.6)	27 (1.0)
Active joint count	152 (6.8)	–	257 (9.8)	–
Acute-phase reactants	103 (4.6)	–	–	–

* Values are the number (%) unless indicated otherwise. The 2008 criteria for LDA are not met when the physician global assessment of disease activity (PhGA) is >3.4, the parent global assessment is >2.1, or the swollen joint count is >1. The JADAS-10 criteria for LDA are not met when the sum of the scores of the 4 JADAS-10 components (PhGA, parent global assessment, active joint count, and acute-phase reactant) is between 1.1 and 3.8. The cJADAS-10 criteria for LDA are not met when the sum of the scores of the 3 cJADAS-10 components (PhGA, parent global assessment, and active joint count) is between 1.1 and 2.5.
† Observations with discordance/observations with paired assessment of both criteria.

parent global assessment, which is included in the JADAS-10 but not in the 2004 ID criteria. Considering that pain is a major determinant of the parent global assessment and that children with chronic arthritis might have persistent pain symptoms independent of joint inflammation, the researchers argued that the parental assessment might incongruously inflate the JADAS-10, making it an imprecise measure of remission.

However, in a subsequent study aimed to compare short- and long-term outcomes following achievement of ID and LDA on the cJADAS-10 and the 2004 ID criteria in 832 children with JIA, the same group of investigators found that only ID according to the cJADAS-10 was associated with improved functional ability and psychosocial health. This finding suggests that the cJADAS-10 criteria for ID may be superior to the 2004 ID criteria in predicting long-term parent-reported outcomes (17).

We found that the parent global assessment was responsible for the discordance in 8.7–15.5% of patients who met the 2004 or 2011 ID criteria but who did not fulfill the JADAS-10 or cJADAS-10 ID criteria. Although this percentage is sizeable, it is overall comparable to the proportion of instances in which the PhGA (10–12.3%) and the APRs (10.8–17.3%) were involved in the discordance between fulfilment of the JADAS-10 or cJADAS-10 ID criteria and lack of fulfillment of the 2004 or 2011 ID criteria. This finding suggests that, in contrast with the common view, the parent global assessment does not represent the leading driver of discordance among ID definitions.

Another factor that was responsible for divergence between criteria in the study of Shoop-Worral et al (8), as well as in our analysis, was the tendency of some clinicians not to mark their VAS for global assessment at exactly 0, even on resolution of active disease. The disconnection between physicians' judgment and actual disease state was underscored in our study by the almost negligible impact on discordance of the active joint count. This finding suggests that the physicians do not base their judgment of disease quiescence only on joint assessment. This drawback has been noticed previously and has led to modification of the criteria for ID in some recent therapeutic studies by setting the minimum score of the PhGA at 1 (18,19) or even at 2 (20). Notably, the occurrence of this phenomenon in our study with the use of the 21-circle VAS (16), which is thought to avoid the aversion to extremes often seen on the horizontal line VAS (21), indicates that it does not depend on the type of VAS used.

The prominent role of APRs in determining discordance between the JADAS-10 and the 2004 and 2011 definitions of ID highlights the need to further investigate the relationship between physician- and parent-perceived remission and remission assessed by objective measures of inflammatory activity. Future studies should also evaluate whether the traditional APRs can be replaced by modern biomarkers of immune activation and systemic inflammation or by imaging methods, which may represent more reliable indicators of biologic remission.

Our study should be interpreted in the light of some potential caveats. We recognize that the placement of the ILAR categories into the functional phenotypes of oligoarthritis and polyarthritis was arbitrary and not based on the count of affected joints over time. However, this information was unavailable for most patients. The design of our study did not allow us to compare the capacity of criteria to predict future flares or long-term disease outcomes, such as radiographic joint damage or functional disability. In addition, we could not address the role of biomarkers or imaging methods, which may define disease remission more reliably than clinical assessment. Finally, the impact on parental discordance of factors unrelated to disease activity, such as fibromyalgia, mechanical pain, or impaired physical function or quality of life, could not be assessed. The main strengths of our analysis are the large patient sample and the comprehensive assessment of existing definitions.

In conclusion, we found fair concordance between definitions of ID and LDA based on multiple criteria and composite disease activity scores. This observation suggests that there is a large overlap in the patient groups identified by the 2 types of criteria. The fact that the main drivers of discordance between criteria were PhGA and parent global assessment and APRs calls for further studies aimed to investigate the impact on the definition of ID of physician and parent subjective perceptions of disease remission and of remission assessed by laboratory measures of inflammatory activity.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ravelli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Giancane, Ruperto, Consolaro, Ravelli.
Acquisition of data. Campone, Gicchino, Bava, Rosina, Boyko, Martin, El Miedany, Harjacek, Hashad, Ioseliani, Burgos-Vargas, Joos, Scott, Manel, Ayala, Ekelund, Al-Abrawi, Aiche, Norambuena, Melo-Gomes.
Analysis and interpretation of data. Giancane, Campone, Alongi, Ruperto, Consolaro, Ravelli.

REFERENCES

1. Lovell DJ, Ruperto N, Giannini EH, Martini A. Advances from clinical trials in juvenile idiopathic arthritis. Nat Rev Rheumatol 2013;9:557–63.
2. Ravelli A, Consolaro A, Horneff G, Laxer RM, Lovell DJ, Wulffraat NM, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis 2018;77:819–28.
3. Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31:2290–4.
4. Wallace CA, Giannini EH, Huang B, Itert L, Ruperto N, for the Childhood Arthritis and Rheumatology Research Alliance (CARRA), the Pediatric Rheumatology Collaborative Study Group (PRCSG), and the Paediatric Rheumatology International Trials Organisation (PRINTO). American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2011;63:929–36.
5. Magni-Manzoni S, Ruperto N, Pistorio A, Sala E, Solari N, Palmisani E, et al. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. Arthritis Rheum 2008;59:1120–7.
6. Consolaro A, Bracciolini G, Ruperto N, Pistorio A, Magni-Manzoni S, Malattia C, et al. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the Juvenile Arthritis Disease Activity Score. Arthritis Rheum 2012;64:2366–74.
7. Consolaro A, Negro G, Chiara Gallo M, Bracciolini G, Ferrari C, Schiappapietra B, et al. Defining criteria for disease activity states in nonsystemic juvenile idiopathic arthritis based on a three-variable Juvenile Arthritis Disease Activity Score. Arthritis Care Res (Hoboken) 2014;66:1703–9.
8. Shoop-Worral SJ, Verstappen SM, Baildam E, Chieng A, Davidson J, Foster H, et al. How common is clinically inactive disease in a prospective cohort of patients with juvenile idiopathic arthritis? The importance of definition. Ann Rheum Dis 2017;76:1381–8.
9. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–2.
10. Filocamo G, Consolaro A, Schiappapietra B, Dalprà S, Lattanzi B, Magni-Manzoni S, et al. A new approach to clinical care of juvenile idiopathic arthritis: the Juvenile Arthritis Multidimensional Assessment Report. J Rheumatol 2011;38:938–53.
11. Verazza S, Davì S, Consolaro A, Bovis F, Insalaco A, Magni-Manzoni S, et al. Disease status, reasons for discontinuation and adverse events in 1038 Italian children with juvenile idiopathic arthritis treated with etanercept. Pediatr Rheumatol Online J 2016;14:68.
12. Consolaro A, Giancane G, Alongi A, van Dijkhuizen EH, Aggarwal A, Al-Mayouf SM, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. Lancet Child Adolesc Health 2019;3:255–63.
13. Bazso A, Consolaro A, Ruperto N, Viola S, Magni-Manzoni S, Malattia C, et al. Development and testing of reduced joint counts in juvenile idiopathic arthritis. J Rheumatol 2009;36:183–90.
14. Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009;61:658–66.
15. Nordal EB, Zak M, Aalto K, Berntson L, Fasth A, Herlin T, et al. Validity and predictive ability of the juvenile arthritis disease activity score based on CRP versus ESR in a Nordic population-based setting. Ann Rheum Dis 2012;71:1122–7.
16. Filocamo G, Davì S, Pistorio A, Bertamino M, Ruperto N, Lattanzi B, et al. Evaluation of 21-numbered circle and 10-centimeter horizontal line visual analog scales for physician and parent subjective ratings in juvenile idiopathic arthritis. J Rheumatol 2010;37:1534–41.
17. Shoop-Worrall SJ, Verstappen SM, McDonagh JE, Baildam E, Chieng A, Davidson J, et al. Long-term outcomes following achievement of clinically inactive disease in juvenile idiopathic arthritis: the importance of definition. Arthritis Rheumatol 2018;70:1519–29.
18. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2385–95.
19. Otten MH, Prince FH, Armbrust W, ten Cate R, Hoppenreijs EP, Twilt M, et al. Factors associated with treatment response to etanercept in juvenile idiopathic arthritis. JAMA 2011;306:2340–7.
20. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008;372:383–91.
21. Taylor J, Giannini EH, Lovell DJ, Huang B, Morgan EM. Lack of concordance in interrater scoring of the provider's global assessment of children with juvenile idiopathic arthritis with low disease activity. Arthritis Care Res (Hoboken) 2018;70:162–6.

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Time to First Completed Visit and Health Care Utilization Among Young Adults Transferring From Pediatric to Adult Rheumatologic Care in a Safety-Net Hospital

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Objective. The transfer from pediatric to adult care for young adults is a vulnerable period. Our objectives were to quantify the time between the final pediatric and the first adult visit and to evaluate unscheduled utilization in care and progression to end-stage renal disease (ESRD) or death.

Methods. We conducted a retrospective analysis of pediatric patients transferring to a large adult rheumatology clinic. Outcomes included time to first completed adult visit, unscheduled health care utilization (hospitalizations and emergency department [ED] visits), and progression to ESRD or death. Multivariable regression models assessed variables predictive of outcomes of interest.

Results. A total of 141 pediatric patients who transferred care were identified: 77% female, 65% Hispanic, and 60% with connective tissue diseases (CTDs). The mean time between final pediatric and first completed adult rheumatology visit was 221 days (range 0–1,207 days). In regression modeling, we found that continued insurance coverage, younger age at referral, and referral from a pediatric rheumatologist were predictive of shorter time to completed adult visit ($P < 0.005$). Factors associated with hospitalizations and ED visits included CTD diagnosis and Black race (odds ratio [OR] 8.54 [95% confidence interval (95% CI) 1.84–39.58] and 3.04 [95% CI 1.02–9.12] for hospitalizations and OR 3.6 [95% CI 1.59–8.14] and 6.0 [95% CI 1.60–22.69] for ED visits, respectively). ESRD or death occurred among 15% of patients with a CTD.

Conclusion. In pediatric patients transferring to an adult rheumatology clinic, continued insurance coverage and referral from a pediatric rheumatologist decreased delays in attending an adult visit; CTD and Black race were associated with high rates of unscheduled health care utilization.

INTRODUCTION

The Institute of Medicine has identified the transition from pediatric to adult care as an important issue to the health and well-being of young adults, in particular among those patients with chronic diseases (1). Young adults ages 18–25 years have worse health outcomes compared to youth ages 12–17 years or adults ages 26–34 years (2). Barriers to a successful transfer from pediatric to adult care include lack of communication and coordination of care between pediatric and adult health care systems, gaps in health insurance/health coverage, inadequate patient self-advocacy and self-management skills, and lack of family and social support systems (3).

Patients with chronic childhood-onset illnesses are at high risk for being lost to follow-up during the transition period (4), which may translate into higher health care utilization, damage accrual, and mortality (5–7). While the transfer of care to an adult system can be a high-risk time for any young adult with a chronic illness, socioeconomically disadvantaged youths have even worse outcomes than the general population (8). Thus, the importance of a successful transition to adult care within the pediatric rheumatology community is increasingly recognized as a metric of good care (3,9,10).

Most studies assessing transfer of care have focused on engagement and retention in care (11); however, studies among patients with rheumatic diseases are limited (9,12), and knowledge gaps remain about post-transfer outcomes among youths with rheumatic conditions, especially among those from sociodemographically vulnerable backgrounds. Improved characterization of the transfer period and of factors associated with time

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SIGNIFICANCE & INNOVATIONS

- The time for transfer between pediatrics and the completed adult rheumatology visit is reduced if the referring physician is a pediatric rheumatologist and insurance coverage is maintained.
- Pediatric patients with a connective tissue disease or of Black race are particularly vulnerable to unscheduled hospitalizations and emergency department visits following transfer to adult care.

to first completed adult visit and with unscheduled health care utilization merit further inquiry.

The objectives of this study were to evaluate the transfer of care from pediatric to adult rheumatology. In particular, we were interested in assessing factors that resulted in increased time to first adult visit and factors that impacted adverse health outcomes, including unscheduled health care utilization during the first year in adult care and progression to end-stage renal disease (ESRD) or death. Demographic variables, disease categories, and potentially modifiable factors such as communication between clinicians were preselected as independent variables.

PATIENTS AND METHODS

Study design and population. We performed a retrospective analysis of patients who transferred from pediatric to adult rheumatology in a large hospital system. Patients referred to our adult rheumatology clinic at Dallas County's safety-net hospital system were identified based on being age ≤21 years at the time of referral. Those who were previously seen by a pediatric rheumatologist on at least 2 occasions were included if they had a doctor-diagnosed rheumatic condition. We received approval from the University of Texas Southwestern Medical Center Internal Review Board for retrospective chart analysis.

Outcomes. Outcomes of interest were the time between referral and appointment in the adult system as well as the time between final pediatric visit and first completed adult visit. We evaluated the proportion of patients with unscheduled hospitalizations and emergency department (ED) visits within 365 days from the final pediatric visit. Patients with <180 days since the final pediatric visit were excluded from analysis. Planned hospitalizations such as renal biopsies or uncomplicated deliveries were excluded. Progression to ESRD and death were also assessed.

Independent variables. We collected demographic data (age at referral, sex, race/ethnicity), referring physician (pediatric rheumatologist versus other; see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24409/abstract), and diagnosis (determined from review of electronic health records [EHRs]). Diagnoses were grouped into connective tissue diseases (CTDs), juvenile idiopathic arthritis (JIA), or other (comprised of vasculitides, isolated uveitis, sarcoidosis, and autoinflammatory syndromes). Further diagnostic characterization can be found in Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24409/abstract. We assessed direct communication that occurred between pediatric and adult clinicians as documented in the EHR. The type of insurance at referral was categorized into none, private insurance, and publicly funded insurance (which included Medicaid, a state-administered program for low-income individuals that in the state of Texas terminates at age 19 years, unless there is established disability status; the Children's Health Insurance Program, which similarly terminates at age 19 years; Children with Special Health Care Needs (a Title V program that terminates at age 21 years); and Dallas County funding for care within our hospital system.

Additional variables included whether patients had an insurance lapse of >30 days between their final pediatric and first completed adult visit, and whether an overlapping adult visit took place before the final pediatric visit occurred (the patient was seen by an adult rheumatologist prior to discharge from pediatric care). Dedicated appointment slots were created in the adult rheumatology clinic and a protocolized referral process was used in which a centralized contact person was identified for receipt of referrals from the pediatric rheumatology clinics in our county. This alternate referral process, which has been used uniformly since January 2018, was also analyzed.

Statistical analysis. The statistical approaches used descriptive, comparison, and multivariable regression analysis to determine the factors that characterize the transition of pediatric patients to adult rheumatology. Categorical data items such as sex, race/ethnicity, diagnosis, and insurance were summarized using frequency counts and percentages, while means ± SDs were calculated for numerical values such as age. Factors influencing the time from referral to first scheduled appointment and time from pediatric to first completed adult visit as well as unscheduled health care utilization (hospitalizations, ED visits) and death/ESRD were compared with *t*-tests for independent comparisons, one-way analysis of variance, and chi-square contingency analysis as indicated. No adjustments were made for multiple comparisons. Missing observations reduced the sample sizes for some of the measurements.

A stepwise multiple linear regression model to predict time from final pediatric to completed adult visit and stepwise logistic regression models to predict unscheduled hospitalizations or ED visits within 365 days of the final pediatric visit used the following variables as possible predictors: sex, race/ethnicity, diagnosis, referral source, loss of insurance, alternate referral process, and evidence of communication between pediatric and adult physicians in the medical record. Indicator variables were created

for race/ethnicity and diagnostic categories. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were determined for each measurement in logistic regression models. The Hosmer-Lemeshow test was used to assess the fit of the resulting logistic regression models. Statistical analyses were carried out using SAS software, version 9.4. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Demographic characteristics. Between January 1, 2011 and June 30, 2019, 380 patients were identified, ages 17–21 years, who were referred to the adult rheumatology clinic at our county's large safety-net hospital system. Of the 380 patients identified, 171 (45%) were found to have a childhood-onset rheumatic condition. Twenty patients were excluded because they had a visit with another adult rheumatologist prior to referral to our clinic. One patient was excluded because she had never been seen by a pediatric rheumatologist. Nine patients were excluded because they had incomplete data in the EHR. Data from 141 patients were analyzed.

Of the 141 patients, 77% were female, 65% were Hispanic, 21% were Black, and 14% were White or Asian (Table 1). Sixty percent had a CTD (81% of these had systemic lupus erythematosus [SLE]) and 30% had JIA (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24409/abstract). A total of 77% of referrals to adult rheumatology came from a pediatric rheumatologist; the remainder came from urgent or primary care physicians (10%), emergency room physician or hospitalist (10%), maternal fetal medicine (3%), and other specialists (1%) (see Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24409/abstract). Of those patients who did not receive a referral to adult care from a pediatric rheumatologist, at least half were not formally discharged from pediatric care and an additional 20% were from outside the region. The mean age at referral was 18.3 years for patients referred from pediatric rheumatology and 19.6 years for patients referred by other clinicians. Overlapping visits (pediatric followed by adult followed by final pediatric visit) occurred 19% of the time. The alternate referral process was employed for 34% of patients. Almost all patients (91%) had public insurance at the time of referral, 9% had no funding, and <1% had private insurance. One-third of patients (33%) had a lapse in insurance coverage of >30 days between pediatric and completed adult visits. Six patients left pediatric care because of a coexisting pregnancy (mean age 17.4 years); an additional 3 patients were referred by obstetrics during pregnancy after being lost to follow-up from pediatric care (mean age 20.4 years).

Table 1. Demographic characteristics of pediatric patients transitioning to adult rheumatology clinic (n = 141)*

Characteristic	Value
Sex	
Female	109 (77)
Male	32 (23)
Race/ethnicity	
Hispanic	92 (65)
Black	30 (21)
White	14 (10)
Asian	5 (4)
Diagnoses	
Connective tissue diseases	85 (60)
Juvenile idiopathic arthritis	43 (30)
Other rheumatic disease	13 (9)
Age at referral, mean ± SD years	
Referral by pediatric rheumatology	18.3 ± 0.5
Referral by all others	19.6 ± 1.08
Referring clinician	
Pediatric rheumatologist	108 (77)
All other clinicians	33 (23)
Documented communication	
No	124 (88)
Yes	17 (12)
Overlapping adult visit	
No	114 (81)
Yes	27 (19)
Referral process	
Usual process	93 (66)
Alternate referral process	48 (34)
Primary coverage at referral	
Medicaid	90 (64)
CHIP	11 (8)
Title V funding	13 (9)
County funding	14 (10)
No coverage	12 (9)
Insurance lapse between pediatric and adult visits	
No	94 (67)
Yes	47 (33)

* Values are the number (%) unless indicated otherwise. CHIP = Children's Health Insurance Program.

Time to completed adult visit. The mean ± SD time between referral placement and the first scheduled appointment was 135 ± 115 days (range 2–694 days). The mean ± SD time between final pediatric visit and first completed adult visit was 221 ± 264 days (range 0–1,207 days). Patients who had a statistically significant shorter time period between pediatric and first completed adult visit were more likely to have been referred by a pediatric rheumatologist versus any other clinician (mean 144 versus 529 days; $P < 0.0001$) (Figure 1A), were more likely to have documented communication between pediatric and adult rheumatologists (mean 82 versus 242 days; $P = 0.02$) (Figure 1B), were more likely to have had insurance at referral (mean 209 versus 382 days; $P = 0.046$) (Figure 1C), were more likely to have maintained insurance coverage between pediatric and adult visits versus a lapse in coverage of longer than 30 days (mean 116 versus 499 days; $P < 0.0001$) (Figure 1D), and were more likely to have had an overlapping adult visit before the final pediatric visit (mean 74 versus 259 days; $P = 0.001$) (Figure 2A).

Those who had at least 1 overlapping adult visit before being discharged from pediatric care were more likely to have

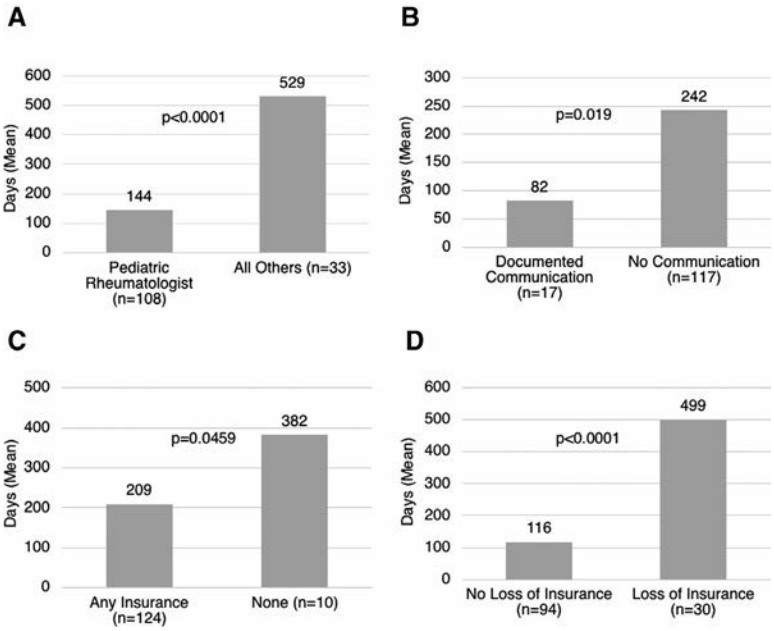

Figure 1. **A**, Time from pediatric to completed adult visit by referring physician; **B**, Time from pediatric to completed adult visit by communication; **C**, Time from pediatric to completed adult visit by insurance at referral; **D**, Time from pediatric to completed adult visit by loss of insurance.

decreased time between pediatric and completed adult visits ($P = 0.001$), were more likely to have been referred to care by a pediatric rheumatologist ($P = 0.007$), and were less likely to have insurance gaps between final pediatric and first adult visit (11% versus 31%; $P = 0.04$).

Those patients who transferred care using the alternate referral process had significantly decreased mean time between referral and first scheduled visit, 162 versus 83 days ($P < 0.0001$) and mean time from pediatric to first completed adult visit, 279 versus 112 days ($P = 0.0004$) (Figure 2B). Sex, race/ethnicity, and diagnosis did not impact time to visit.

In a stepwise linear regression model of time between final pediatric and first completed adult visit, the following variables were predictive of a shorter time to completed visit: continued insurance coverage between pediatric and adult care ($P < 0.0001$), referral by a pediatric rheumatologist ($P = 0.0025$), and younger age at referral ($P = 0.0008$) (Table 2). This model resulted in an R^2 of 0.55, with continued insurance coverage accounting for most of the variation ($R^2 = 0.39$).

Hospitalizations. Twenty-six percent of patients had unscheduled hospitalizations within a year of the final pediatric visit. Hospitalizations occurred in 52% of Black patients, 21% of Hispanic patients, and 6% of White or Asian patients ($P = 0.0005$) (Figure 3A). Hospitalizations occurred among 39% of patients with a CTD, 8% of those with other rheumatic diseases, and 5% of those with JIA ($P = 0.0001$) (Figure 3B). Twenty percent of patients who were referred to adult care by a pediatric rheumatologist had hospitalizations compared to 45% of patients whose referral came from other sources ($P = 0.004$) (Figure 4A). Patients without insurance coverage at the time of referral or who lost their insurance for >30 days between final pediatric and first adult visit were more likely to be hospitalized ($P < 0.05$) (Figures 4B and 4C). Patients who transferred using the alternate referral process

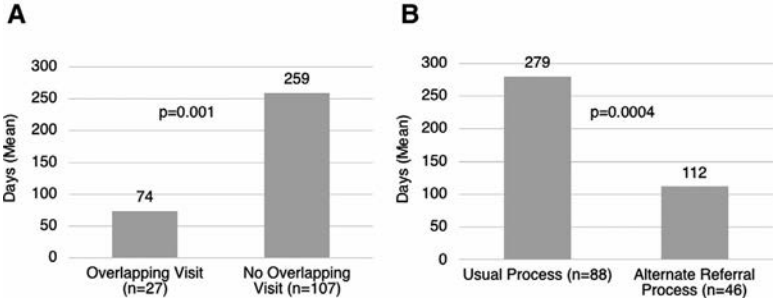

Figure 2. **A**, Time from pediatric to completed adult visit by overlapping adult visit; **B**, Time from pediatric to completed adult visit by referral process.

Table 2. Predictors of time to first adult visit and unscheduled health care utilization by stepwise regression model*

Predictor	Value	*P*
Time from final pediatric to first adult visit†		
Insurance loss	239 (163–316)	<0.0001
Referral by non-pediatric rheumatologist	156 (56–256)	0.0025
Age at referral	86 (37–135)	0.0008
Hospitalizations within 365 days of final pediatric visit‡		
CTD diagnostic category	8.54 (1.84–39.58)	0.0002
Black race	3.04 (1.02–9.12)	0.04
ED visits within 365 days of final pediatric visit‡		
CTD diagnostic category	3.60 (1.59–8.14)	<0.0001
Black race	6.02 (1.60–22.69)	0.004

* CTD = connective tissue disease; ED = emergency department.
† Coefficient (95% confidence interval [95% CI]) by multiple linear regression.
‡ Odds ratio (95% CI) by multiple logistic regression.

had fewer hospitalizations within a year of the pediatric visit (31% versus 13%; *P* = 0.02) (Figure 4D). Those who were hospitalized were older at the time of referral (mean age 18.88 versus 18.45 years; *P* = 0.009).

In a stepwise logistic regression model, the presence of a CTD and Black race were significantly associated with hospitalization (OR 8.54 [95% CI 1.84–39.58], *P* = 0.0002 and OR 3.04 [95% CI 1.015–9.121], *P* = 0.04, respectively) (Table 2). This model provided a good fit (*P* = 0.3) by the Hosmer-Lemeshow goodness-of-fit test.

ED visits. Over half of patients (53%) had ED visits within a year of the final pediatric visit. Patients were more likely to have ED visits based on their race/ethnicity (83% of Blacks, 46% of Hispanics, and 39% of Whites or Asians; *P* = 0.001) (Figure 3A), their diagnostic category (69% of patients with a CTD, 42% of patients with other rheumatologic diagnoses, and 27% of patients with JIA; *P* < 0.0001) (Figure 3B), and lack of insurance at referral (*P* < 0.0092) (Figure 4B). Factors not contributing to ED visits included referring physician, loss of insurance between final pediatric and first completed adult visit, alternate referral process, sex, age, and communication between pediatric and adult physicians (Figure 4).

In a stepwise logistic regression model, Black race and the presence of a CTD were significantly associated with ED visits (OR 6.02 [95% CI 1.598–22.69], *P* = 0.004, and OR 3.6 [95% CI 1.588–8.141], *P* = 0.001, respectively). Goodness of fit of this model was excellent (*P* = 0.98) by a Hosmer-Lemeshow goodness-of-fit test.

Death and ESRD. Five deaths occurred following transfer to adult care. Eight patients developed ESRD, 7 of whom had normal renal function at the final pediatric visit and 1 whose estimated glomerular filtration rate was 30 ml/minute prior to transfer to adult care. Variables that were more common among those who died or progressed to ESRD included older age at referral (19.2 versus 18.5 years; *P* = 0.005), race/ethnicity (23% of Blacks, 5% of Hispanics, and 5% of White or Asian patients; *P* = 0.01), and diagnosis of CTD (occurring only among those with SLE or SLE/systemic sclerosis diagnosis; *P* = 0.006). Patients who developed ESRD or died were more likely to be referred by a physician other than a pediatric rheumatologist (*P* = 0.0007), to lack insurance coverage at the time of referral (*P* = 0.0001), or to lose their insurance between the pediatric and completed adult visits (*P* = 0.002).

DISCUSSION

In our cohort of 141 pediatric patients transferring to adult care, we described prolonged times between the final pediatric and first completed adult rheumatology visits. Factors resulting in shorter time to adult care included a referral by a pediatric rheumatologist, communication between pediatric and adult physicians, insurance coverage at referral, continued insurance coverage between pediatric and adult visits, and an overlapping adult visit prior to discharge from pediatric care. Identifying dedicated appointment slots for transferring patients and a streamlined referral process significantly reduced the time to adult visit. In regression analysis, continued insurance coverage, younger age at referral, and referral from a pediatric rheumatologist remained significantly associated with a shorter time to visit. In stepwise logistic regression models for hospitalizations and ED visits, only

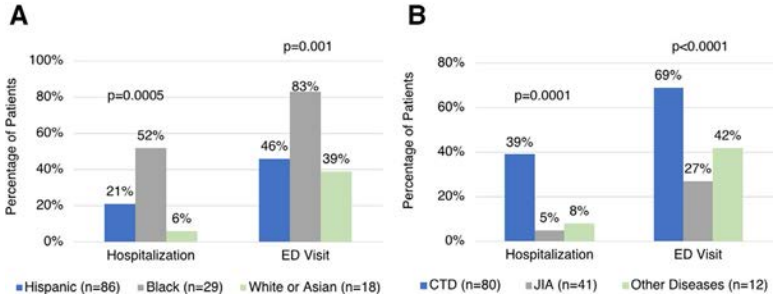

Figure 3. **A**, Utilization by race/ethnicity; **B**, Utilization by disease category. ED = emergency department; CTD = connective tissue disease; JIA = juvenile idiopathic arthritis.

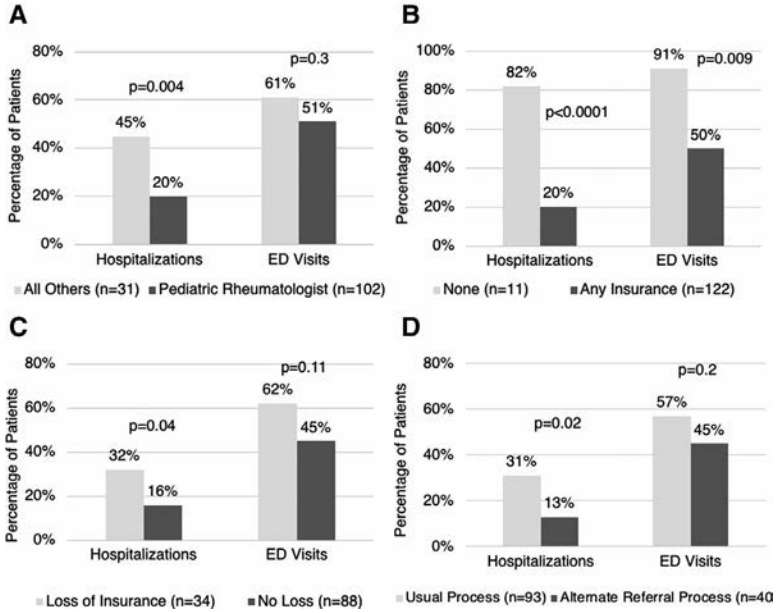

Figure 4. **A**, Utilization by referring physician; **B**, Utilization by insurance at referral; **C**, Utilization by loss of insurance; **D**, Utilization by referral process. ED = emergency department.

CTD diagnosis and Black race were identified as factors leading to increased health care utilization. ESRD and death were common and occurred exclusively among those with a CTD diagnosis. Black race, lack of insurance coverage at the time of referral, and loss of insurance coverage were more common with these adverse outcomes.

Though data are limited on transition in rheumatic disease, up to half of patients with chronic childhood-onset conditions, including JIA, do not establish care with an adult rheumatologist (12–18). One small study found that patients with SLE waited an average time from pediatric to adult care of 253 ± 392 days (19). Similarly, in our cohort, which included patients with all rheumatic diagnoses, the average time between pediatric and adult visits was 221 days. Additional research and innovative clinical programs are needed because pediatric rheumatologists have identified establishing care with an adult physician within 6 months as an important outcome (20).

Existing literature in chronic diseases suggests that insurance type may impact successful transition. Youths with Medicaid as their primary insurance report that the systems in place do not prepare them for transition to adult care (21). Having public insurance is a risk factor for delayed transfers (22), discontinuity in care, poorer health outcomes (14), and high rates of hospitalizations and ED visits during early adulthood (23–25). Our results, which reflect a population of patients with public or no insurance, corroborate these findings. Lack of insurance and loss of insurance contributed to delays in transfer of care and increase in hospitalizations and ED visits. Maintaining insurance coverage has thus been identified by pediatric rheumatologists as crucial to a successful transition (20,26). Nevertheless, in a cohort of continuously privately insured patients with SLE, over one-fourth still failed to establish adult care within a year of the pediatric visit (27).

Referral from a pediatric rheumatologist improves establishment of care with an adult physician and may suggest an important tenet of care coordination, in particular for those at risk for loss to follow-up from pediatric care. In our cohort, older age at referral was associated with delays in care; while this finding may be incidental, it is not unique (16). In our setting, such a finding may be reflective of insurance gaps that accompany those age >18 years who are publicly insured.

Communication between pediatric and adult clinicians has been ranked in the top 5 important quality indicators in qualitative studies of transition in other chronic diseases (28). In our cohort, this communication was associated with decreased time between pediatric and adult visits. In addition, an overlapping adult visit prior to discharge from pediatric care shortened the interval between final pediatric and first adult visit. In a study of pediatric patients with other chronic conditions (including sickle cell disease and type 1 diabetes mellitus), an important determinant of care gaps during the transfer period included not meeting the adult physician prior to discharge from pediatric care (28–31).

Our finding of high rates of hospitalizations and ED visits as well as concerning outcomes of death and progression to ESRD among patients with a CTD who transfer to adult care is not surprising. While a recently published study of continuously privately insured patients with SLE did not suggest an increase in acute care visits following transfer to adult care (27), previous studies of pediatric patients with type 1 diabetes mellitus who transfer to adult care demonstrate an increase in hospitalizations and worse acute and chronic complications following transfer (32,33).

Similarly, most deaths among patients with sickle cell disease occurred shortly after transfer to adult care (34,35). Our analysis suggests that the rates of ESRD and death may be impacted by race and having a CTD as well as by factors related to the transfer to adult care, such as referring provider and insurance. Future work is needed to determine whether deaths and ESRD occurring during the transfer period are related to the severity of childhood-onset SLE (36,37) or whether these are in excess of what would be expected and are instead related to a poor transition to adult care (38–40). Further, whether transfer of care during disease quiescence alters outcomes will also be important to determine.

While racial and ethnic minorities are known to be at increased risk of poorer health outcomes generally, including transition-related outcomes (8), we do not have a clear understanding of why patients of Black race in our cohort had increased hospitalizations and ED visits. This finding warrants further exploration. Understanding the various drivers of health care utilization among diverse patients will be critical to developing appropriate and relevant transition programs. While few interventions have effectively improved outcomes among patients transitioning to adult care in rheumatology (12,41), the implementation of a structured transition process involving key stakeholder input is known to improve outcomes (42,43). The clinical process change within our system, with dedicated appointment slots for transferring patients and protocolization of the referral process, decreased the time to appointment and decreased hospitalizations. This low-complexity, low-cost, and readily implementable approach may have been effective in part because it brought involved stakeholders together in our adult and pediatric rheumatology groups.

Our data have several limitations. The findings in this study represent a single center and may not be generalizable to the broader rheumatologic pediatric population. We extracted data by review of available medical records in our EHR. Thus, we may have missed hospitalizations and ED visits that were not identifiable through our system or communication between physicians that was not documented. Inasmuch as the majority of pediatric patients in our area who have public insurance or no insurance transfer subspecialty care to our hospital system, we may have missed patients who successfully transferred to adult care in other systems. Furthermore, we may have excluded patients who were referred to care after age 21 years or who have yet to establish care with an adult rheumatologist (12–18). Despite these limitations, this well-defined, racially diverse cohort provides important descriptive factors that may help produce better strategies for reducing wait times and targeting vulnerable groups to reduce unscheduled health care utilization.

A recent Cochrane review concluded that there are few rigorously tested interventions in the field of transition of care for young adults with chronic illnesses, and this gap is an area of great need and opportunity (44). Our findings have several important implications and identify potentially modifiable factors that can be addressed using process improvement at a systems level: 1) referral from a pediatric rheumatologist may be an important component of care coordination that prevents patients from being lost to follow-up from the pediatric system, 2) creating designated adult patient slots with a streamlined referral protocol can improve this process, and 3) overlapping an adult visit prior to discharge from pediatric care may be one possible pathway to ensure that patients have established adult care and could encourage and reinforce communication between clinicians.

Our findings that disease characteristics (CTD diagnosis) and Black race were associated with hospitalizations and ED visits suggest that additional efforts are needed to specifically target these vulnerable populations when transferring care. Developing a registry that tracks patients through the transition process has been recommended by the Center for Health Care Transition Improvement's Got Transition Initiative and may ensure that patients have not dropped off from pediatric care. Finally, the importance of addressing the insurance needs and potential insurance gaps in this population cannot be overemphasized and should be part of the discussion with youths and their families while still under pediatric care, as well as in the public discourse at a policy level (45).

Patients with chronic rheumatic illnesses transferring from pediatric to adult care are a vulnerable population. We found that length of time between a pediatric and completed adult visit is influenced by the patient's referral by a pediatric rheumatologist, communication between pediatric and adult clinicians, insurance gaps, establishing care with an adult physician prior to discharge from the pediatric clinic, and using an alternate referral process to adult rheumatology. Black race and CTD were associated with increased hospitalizations and ED visits in this population and suggest particularly high-risk patients who should be targeted for an improved transition processes. Future plans include improving transition-related discussions and transition readiness in our pediatric clinics, because transition from pediatric to adult care is important not only to the health and well-being of patients with chronic childhood-onset illnesses but also to reduce unnecessary health care utilization.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Bitencourt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bitencourt, Bermas, Makris, Wright, Reisch, Solow.
Acquisition of data. Bitencourt.
Analysis and interpretation of data. Bitencourt, Bermas, Makris, Wright, Reisch, Solow.

REFERENCES

1. Bonnie RJ, Stroud C, Breiner H, editors. Investing in the health and well-being of young adults. Washington (DC): National Academies Press; 2015.
2. Neinstein LS, Irwin CE Jr. Young adults remain worse off than adolescents. J Adolesc Health 2013;53:559–61.
3. Sadun RE, Schanberg LE. Transition and transfer of the patient with paediatric-onset lupus: a practical approach for paediatric and adult rheumatology practices. Lupus Sci Med 2018;5:e000282.
4. Mackie AS, Ionescu-Ittu R, Therrien J, Pilote L, Abrahamowicz M, Marelli AJ. Children and adults with congenital heart disease lost to follow-up: who and when? Circulation 2009;120:302–9.
5. Lim LS, Pullenayegum E, Lim L, Gladman D, Feldman B, Silverman E. From childhood to adulthood: the trajectory of damage in patients with juvenile-onset systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2017;69:1627–35.
6. Fortuna RJ, Robbins BW, Mani N, Halterman JS. Dependence on emergency care among young adults in the United States. J Gen Intern Med 2010;25:663–9.
7. Yeung E, Kay J, Roosevelt GE, Brandon M, Yetman AT. Lapse of care as a predictor for morbidity in adults with congenital heart disease. Int J Cardiol 2008;125:62–5.
8. Lotstein DS, Kuo AA, Strickland B, Tait F. The transition to adult health care for youth with special health care needs: do racial and ethnic disparities exist? Pediatrics 2010;126 Suppl 3:S129–36.
9. Hersh AO, Pang S, Curran ML, Milojevic DS, von Scheven E. The challenges of transferring chronic illness patients to adult care: reflections from pediatric and adult rheumatology at a US academic center. Pediatr Rheumatol Online J 2009;7:13.
10. White PH, Ardoin S. Transitioning wisely: improving the connection from pediatric to adult health care. Arthritis Rheumatol 2016;68:789–94.
11. Rachas A, Lefeuvre D, Meyer L, Faye A, Mahlaoui N, de La Rochebrochard E, et al. Evaluating continuity during transfer to adult care: a systematic review. Pediatrics 2016;138:e20160256.
12. Hazel E, Zhang X, Duffy CM, Campillo S. High rates of unsuccessful transfer to adult care among young adults with juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2010;8:2.
13. Montano CB, Young J. Discontinuity in the transition from pediatric to adult health care for patients with attention-deficit/hyperactivity disorder. Postgrad Med 2012;124:23–32.
14. Garvey KC, Wolpert HA, Rhodes ET, Laffel LM, Kleinman K, Beste MG, et al. Health care transition in patients with type 1 diabetes: young adult experiences and relationship to glycemic control. Diabetes Care 2012;35:1716–22.
15. Reid GJ, Irvine MJ, McCrindle BW, Sananes R, Ritvo PG, Siu SC, et al. Prevalence and correlates of successful transfer from pediatric to adult health care among a cohort of young adults with complex congenital heart defects. Pediatrics 2004;113 Pt 1:e197–205.
16. Andemariam B, Owarish-Gross J, Grady J, Boruchov D, Thrall RS, Hagstrom JN. Identification of risk factors for an unsuccessful transition from pediatric to adult sickle cell disease care. Pediatr Blood Cancer 2014;61:697–701.
17. Wojciechowski EA, Hurtig A, Dorn L. A natural history study of adolescents and young adults with sickle cell disease as they transfer to adult care: a need for case management services. J Pediatr Nurs 2002;17:18–27.
18. Gleeson H, Davis J, Jones J, O'Shea E, Clayton PE. The challenge of delivering endocrine care and successful transition to adult services in adolescents with congenital adrenal hyperplasia: experience in a single centre over 18 years. Clin Endocrinol (Oxf) 2013;78:23–8.
19. Son MB, Sergeyenko Y, Guan H, Costenbader KH. Disease activity and transition outcomes in a childhood-onset systemic lupus erythematosus cohort. Lupus 2016;25:1431–9.
20. Chira P, Ronis T, Ardoin S, White P. Transitioning youth with rheumatic conditions: perspectives of pediatric rheumatology providers in the United States and Canada. J Rheumatol 2014;41:768–79.
21. Sawicki GS, Garvey KC, Toomey SL, Williams KA, Hargraves JL, James T, et al. Preparation for transition to adult care among Medicaid-insured adolescents. Pediatrics 2017;140: e20162768.
22. Fortuna RJ, Halterman JS, Pulcino T, Robbins BW. Delayed transition of care: a national study of visits to pediatricians by young adults. Acad Pediatr 2012;12:405–11.
23. Shankar SM, Arbogast PG, Mitchel E, Cooper WO, Wang WC, Griffin MR. Medical care utilization and mortality in sickle cell disease: a population-based study. Am J Hematol 2005;80:262–70.
24. Wolfson JA, Schrager SM, Coates TD, Kipke MD. Sickle-cell disease in California: a population-based description of emergency department utilization. Pediatr Blood Cancer 2011;56:413–9.
25. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. JAMA 2010;303:1288–94.
26. Hilderson D, Moons P, Westhovens R, Wouters C. Attitudes of rheumatology practitioners toward transition and transfer from pediatric to adult healthcare. Rheumatol Int 2012;32:3887–96.
27. Chang JC, Knight AM, Lawson EF. Patterns of health care utilization and medication adherence among youth with systemic lupus erythematosus during transfer from pediatric to adult care. J Rheumatol 2021;48:105–13.
28. Sobota AE, Shah N, Mack JW. Development of quality indicators for transition from pediatric to adult care in sickle cell disease: a modified Delphi survey of adult providers. Pediatr Blood Cancer 2017;64.
29. Kipps S, Bahu T, Ong K, Ackland FM, Brown RS, Fox CT, et al. Current methods of transfer of young people with type 1 diabetes to adult services. Diabet Med 2002;19:649–54.
30. Reiss JG, Gibson RW, Walker LR. Health care transition: youth, family, and provider perspectives. Pediatrics 2005;115:112–20.
31. Goossens E, Bovijn L, Gewillig M, Budts W, Moons P. Predictors of care gaps in adolescents with complex chronic condition transitioning to adulthood. Pediatrics 2016;137:e20152413.
32. Findley MK, Cha E, Wong E, Faulkner MS. A systematic review of transitional care for emerging adults with diabetes. J Pediatr Nurs 2015;30:e47–62.
33. Nakhla M, Daneman D, To T, Paradis G, Guttmann A. Transition to adult care for youths with diabetes mellitus: findings from a universal health care system. Pediatrics 2009;124:e1134–41.
34. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood 2010;115:3447–52.
35. DeBaun MR, Telfair J. Transition and sickle cell disease. Pediatrics 2012;130:926–35.
36. Ambrose N, Morgan TA, Galloway J, Ionnoau Y, Beresford MW, Isenberg DA, et al. Differences in disease phenotype and severity in SLE across age groups. Lupus 2016;25:1542–50.

37. Hersh AO, von Scheven E, Yazdany J, Panopalis P, Trupin L, Julian L, et al. Differences in long-term disease activity and treatment of adult patients with childhood- and adult-onset systemic lupus erythematosus. Arthritis Rheum 2009;61:13–20.
38. Hersh A, von Scheven E, Yelin E. Adult outcomes of childhood-onset rheumatic diseases. Nat Rev Rheumatol 2011;7:290–5.
39. Felsenstein S, Reiff AO, Ramanathan A. Transition of care and health-related outcomes in pediatric-onset systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2015;67:1521–8.
40. Lawson EF, Hersh AO, Trupin L, von Scheven E, Okumura MJ, Yazdany J, et al. Educational and vocational outcomes of adults with childhood- and adult-onset systemic lupus erythematosus: nine years of followup. Arthritis Care Res (Hoboken) 2014;66:717–24.
41. Robertson LP, McDonagh JE, Southwood TR, Shaw KL. British Society of Paediatric and Adolescent Rheumatology. Growing up and moving on: a multicentre UK audit of the transfer of adolescents with juvenile idiopathic arthritis from paediatric to adult centred care. Ann Rheum Dis 2006;65:74–80.
42. Jones MR, Hooper TJ, Cuomo C, Crouch G, Hickam T, Lestishock L, et al. Evaluation of a health care transition improvement process in seven large health care systems. J Pediatr Nurs 2019;47:44–50.
43. Holmes-Walker DJ, Llewellyn AC, Farrell K. A transition care programme which improves diabetes control and reduces hospital admission rates in young adults with type 1 diabetes aged 15–25 years. Diabet Med 2007;24:764–9.
44. Campbell F, Biggs K, Aldiss SK, O'Neill PM, Clowes M, McDonagh J, et al. Transition of care for adolescents from paediatric services to adult health services. Cochrane Database Syst Rev 2016;4:CD009794.
45. Sharma N, O'Hare K, Antonelli RC, Sawicki GS. Transition care: future directions in education, health policy, and outcomes research. Acad Pediatr 2014;14:120–7.

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BRIEF REPORT

Down Syndrome–Associated Arthritis Cohort in the New Childhood Arthritis and Rheumatology Research Alliance Registry: Clinical Characteristics, Treatment, and Outcomes

Jordan T. Jones,[1] Chelsey Smith,[1] Mara L. Becker,[2] and Daniel Lovell,[3] for the CARRA Registry Investigators

Objective. Down syndrome–associated arthritis (DA) is underrecognized, and current therapies used for juvenile idiopathic arthritis (JIA) appear to be poorly tolerated and less effective in patients with DA. The objective of this study was to characterize clinical manifestations and therapeutic preferences in DA compared to JIA, using the new Childhood Arthritis and Rheumatology Research Alliance (nCARRA) registry.

Methods. In a case–control study, between July 2015 and March 2019, patients with a diagnosis of JIA and Down syndrome (DS) were identified and matched by age, sex, and JIA subtype to patients who have JIA without DS. Collected data included demographic characteristics, disease characteristics, laboratory results, treatment exposure, and outcome measures.

Results. A total of 36 children with DA and 165 with JIA were identified. Most patients presented with polyarticular rheumatoid factor–negative disease. At entry into the nCARRA registry, there were minimal differences between the groups, and at the last visit there were significant differences ($P < 0.05$) for multiple outcome measures. Patients with DA and those with JIA had similar therapeutic exposure to disease-modifying antirheumatic drugs (DMARDs) and biologics, but those with DA had more DMARD-related adverse events (93% versus 25%) and biologic therapy ineffectiveness (60% versus 17%).

Conclusion. There was little difference between patients with DA and those with JIA at baseline, and similar therapy was implemented for those in the nCARRA registry; however, at the last visit, the patients with DA had greater disease burden. Additionally, there were more DMARD-related adverse events and biologic ineffectiveness for those patients with DA. More research is needed to determine differences in pathophysiology and optimal therapeutic approaches.

INTRODUCTION

Down syndrome (DS) is one of the most common birth defects in the US (1) and is a chromosomal disorder characterized by an extensive, heterogenous phenotype that results from a dosage imbalance of genes located on human chromosome 21 (2). This imbalance results in unique medical challenges for those with DS, such as an increased incidence of autoimmune conditions (3). Previous reports have suggested a high prevalence of Down syndrome–associated arthritis (DA) in children with DS (4), with a 2–3 year average delay from symptom onset to diagnosis (5). The majority of those with DA present with >5 joints with active arthritis, with a predilection for small joint involvement (4,5). Many patients with DA have inflammatory bone abnormalities noted on

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The Childhood Arthritis and Rheumatology Research Alliance (CARRA) is a North American research organization incorporated in the US as a 501c3 nonprofit. It receives funding from multiple sources, primarily the Arthritis Foundation, as well as research grants from the NIH and the Patient-Centered Outcomes Research Institute, as well as advocacy organizations and industry. The CARRA Registry is sponsored by CARRA and receives funds from Novartis and Roche to support the pharmacosurveillance program.

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- Despite aggressive therapy with disease-modifying antirheumatic drugs (DMARDs) and biologics, the disease burden for children with Down syndrome–associated arthritis (DA) was higher compared to the disease burden in those with juvenile idiopathic arthritis (JIA).
- Current therapies for JIA have been used to treat children with DA and have shown improvements in disease activity, but optimal treatment approach and plan for escalation of therapy remains unclear.
- Compared to patients with JIA, those with DA have more DMARD-related adverse events and more biologic therapy ineffectiveness.

initial imaging studies (4–6), which raises concern for the risk of permanent joint damage and loss of function.

Gaps in knowledge about optimal treatment approaches in DA have resulted in the utilization of treatment algorithms used for juvenile idiopathic arthritis (JIA), with mixed results (5). Many patients with DA require second- and third-line therapies after treatment with nonsteroidal antiinflammatory drugs (NSAIDs) (5). Despite this, there is currently no guidance on treatment approach and escalation of therapy for patients with DA. Disease-modifying antirheumatic drug (DMARD) intolerance (5) and lack of anti–tumor necrosis factor effectiveness (5,6) have inhibited the identification of optimal therapy approaches.

The objective of this study was to characterize clinical manifestations and therapeutic preferences in DA compared to JIA, using the new Childhood Arthritis and Rheumatology Research Alliance (nCARRA) registry (see Appendix A for CARRA registry site principal investigators, subinvestigators, and research coordinators).

PATIENTS AND METHODS

Study population. The CARRA registry is a multicenter, multidisease registry established by pediatric rheumatologists to capture information about different rheumatic diseases with pediatric onset. The initial CARRA registry was established in 2009 and closed in 2014 to establish the nCARRA registry, which began collecting data in July 2015 (7). Subjects are eligible for inclusion into the nCARRA registry if they are <21 years of age, diagnosed with JIA at or before the age of 16 years, and meet clinical criteria for JIA as defined by Edmonton 2001 International League of Associations for Rheumatology (ILAR) criteria for JIA. DS is documented in the nCARRA registry as a coexisting condition. Between the dates of July 2015 and March 2019, patients with a diagnosis of JIA and DS were identified and matched (at a 1:5 ratio) by age, sex, and JIA subtype to patients with a diagnosis of JIA without DS. The present study was approved by the Children's Mercy Kansas City Institutional Review Board and by the CARRA Data and Sample Share Committee.

Data collection. Clinical data in the nCARRA registry were collected from patients/guardians and medical providers using JIA-specific case report forms at the time of enrollment. Data were collected and recorded by the recruiting physician using current clinical history, examination findings, parental information, and chart review. Baseline measures were obtained, and included ILAR classification, laboratory tests, joints with active arthritis and limited range-of-motion (ROM), morning stiffness, radiographic damage, presence of uveitis, physician global assessment of disease activity (10-point Likert scale, where 0 = clinically inactive disease), patient/parent assessment of overall well-being (patient/parent global assessment; 10-point Likert scale, where 0 = very good), and the Childhood Health Assessment Questionnaire (C-HAQ; a disease-specific measure of functional status developed for JIA and used in clinical practice) (8). Regarding therapy, adverse events were defined as a symptom, physical exam finding, abnormal laboratory value, or worsening of preexisting condition due to therapy. Therapy ineffectiveness was defined as a change in medication due to continued active arthritis, independent from adverse events.

Follow-up data was obtained at scheduled follow-up visits (every 6 months) and at time of therapy changes. Data were pooled and stored in a secure centralized electronic database and deidentified prior to analysis.

Disease measurements. There are currently no validated arthritis disease measures for use in DS. The disease measures collected in the nCARRA registry are validated in JIA.

A clinical Juvenile Arthritis Disease Activity Score (cJADAS) (9) was calculated from the collected information. The cJADAS is a composite disease activity score for JIA, and is the sum of the physician global assessment, patient/parent global assessment, and number of joints with active arthritis, capped at a maximum score of 10 (cJADAS-10). The cJADAS-10 has cutoff values for defining states of disease activity. For oligoarticular disease, inactive disease is defined as a cJADAS-10 score of ≤1.0, low disease activity is a score of >1.0 to ≤1.5, moderate disease activity is a score of 1.51 to 4, and high disease activity is a score of >4. For polyarticular disease, inactive disease is defined as a cJADAS-10 score of ≤ 1.0, low disease activity is a score of >1.0 to ≤2.5, moderate disease activity is a score of 2.51 to 8.5, and a score of >8.5 is high disease activity (10). Cutoff values have not been established for other JIA subtypes.

Statistical analysis. Numerical variables were summarized by mean ± SD, and binary and categorical variables were summarized by frequency and percentage. The relationship between outcome variables (physician global assessment, patient/parent global assessment, active arthritis, and limited joint counts, C-HAQ

score, and cJADAS-10 score) between those with and without DS were evaluated by Mann-Whitney U test. All statistical analysis was completed using IBM SPSS Statistics, version 24, software.

RESULTS

Demographic characteristics. Of 7,337 unique JIA patients in the nCARRA registry at the time of this study, 36 were identified with DS and matched by age, sex, and JIA subtype to 165 patients without DS. The mean ± SD follow-up periods for those patients with DS and those without DS were 4.5 ± 3.2 years and 4.7 ± 3.9 years, respectively. The patients in both groups were mostly female (67% of those with DS and 70% of those without DS) and had polyarticular, rheumatoid factor–negative disease (67% of those with and those without DS). The mean ± SD age at arthritis diagnosis was 6.9 ± 3.4 years for those with DS and 7.7 ± 5.8 years for those without DS. There was no significant difference ($P = 0.23$) in mean ± SD time from initial symptom onset to arthritis diagnosis (8.3 ± 9.8 months for those with DS and 9.8 ± 18.7 months for those without DS). Antinuclear antibody (ANA) positivity was present in 33% (12 of 36) of patients with DS and in 57% (86 of 152) of those without DS. Of patients with DS, 44% (16 of 36) had normal laboratory test results (normal markers of inflammation and negative findings for ANA, HLA–B27, and rheumatoid factor) at diagnosis (Table 1).

Table 1. Demographic characteristics of patients with and without Down syndrome (DS) at baseline visit*

Characteristic	DS (n = 36)	Without DS (n = 165)
Female sex	24 (67)	116 (70)
Age at arthritis diagnosis, years (range)	6.9 (2–15)	7.7 (1–17)
Time to diagnosis, months (range)†	8.3 (0–49)	9.8 (0–112)
Arthritis subtype		
Oligoarticular	3 (8)	14 (9)
Polyarticular RF-	24 (67)	115 (67)
Polyarticular RF+	0 (0)	0 (0)
Systemic	1 (3)	5 (3)
Psoriatic	3 (8)	14 (9)
Enthesitis-related	3 (8)	12 (8)
Undifferentiated	2 (6)	5 (4)
Laboratory test‡		
Normal test results§	16 (44)	1 (5)
Elevated antinuclear antibody	12 (33)	86 (57)
Elevated rheumatoid factor	0 (0)	0 (0)
Elevated erythrocyte sedimentation rate	6 (17)	17 (77)
Elevated C-reactive protein	6 (17)	12 (63)
HLA–B27 positivity	2 (11)	21 (24)
Imaging¶		
Damage present	9 (38)	23 (22)
Damage absent	15 (62)	82 (78)
Morning stiffness#		
Yes	14 (45)	84 (51)
No	17 (55)	81 (49)

* Values are the number (%) unless indicated otherwise. RF = rheumatoid factor.
† Time to diagnosis is the time between first documented musculoskeletal symptoms consistent with inflammatory joint disease and diagnosis of arthritis.
‡ Of the patients with DS, 18 were tested for HLA–B27 positivity. Of the students without DS, 19 were tested for all, 152 were tested for elevated antinuclear antibodies, 22 were tested for elevated erythrocyte sedimentation rate, 19 were tested for elevated C-reactive protein level, and 86 were tested for HLA–B27 positivity.
§ Normal is defined as erythrocyte sedimentation rate and C-reactive protein test results in the normal range and antinuclear antibody, RF, and HLA–B27 negativity.
¶ Imaging evidence of damage that was available at diagnosis. Specific imaging modality data were not collected. For imaging, the number of patients with DS = 24, and the number of patients without DS = 105.
# For morning stiffness, the number of patients with DS = 31, and the number of patients without DS = 165.

Imaging and treatment. Of the patients who had radiographic imaging at time of diagnosis (the nCARRA registry does not specify imaging type), 38% (9 of 24) of those with DS and 22% (23 of 105) of those without DS had results that showed radiographic evidence of damage (Table 1).

At diagnosis, there was a significant difference ($P < 0.05$) for initiation of NSAIDs (17% [6 of 36] of patients with DS and 13% [22 of 165] of those without DS), but not for DMARDs (44% [16 of 36] of patients with DS and 32% [52 of 165] of those without DS) or biologic therapy initiation (17% [6 of 36] of patients with DS and 7% [12 of 165] of those without DS) between patients with and without DS. Of the patients with and without DS, 19% (7 of 36 with DS; 32 of 165 without DS) simultaneously began DMARD and biologic therapy. Over the course of treatment, 42% of patients with and without DS (15 of 36 with DS; 70 of 165 without DS) had at least 1 intraarticular glucocorticoid injection. Of patients with DS, 78% (28 of 36) were treated with a DMARD, with methotrexate (100% [28 of 28]) being used by all who were being treated with a DMARD. Leflunomide and azathioprine were other DMARDs that were used. Of the patients without DS, 87% (144 of 165) used a DMARD, with methotrexate being the most used therapy (95% [137 of 144]), followed by hydroxychloroquine (9% [13 of 144]), sulfasalazine (8% [12 of 144]), and leflunomide (7% [10 of 144]).

Of the patients who were treated with DMARDs, 54% (15 of 28) of those with DS and 12% (16 of 136) of those without DS had methotrexate discontinued, with the majority of discontinuations being due to adverse events (93% [14 of 15] in those with DS and 25% [4 of 16] in those without DS) ($P < 0.05$).

Biologic therapy was used in 75% (27 of 36) of patients with DS and 70% (115 of 165) of those without DS. Etanercept was the most used biologic (70% [19 of 27] of patients with DS and 61% [70 of 115] of those without DS), followed by adalimumab (52% [14 of 27] of patients with DS and 59% [68 of 115] of those without DS). More than half of the patients with DS had their biologic therapy (60% [16 of 27]) changed to a different biologic due to ineffectiveness, while 17% (20 of 115) of those without DS had a biologic treatment change due to ineffectiveness. Other biologics used in patients with DS were abatacept (19% [5 of 27]), tocilizumab (19% [5 of 27]), infliximab (4% [1 of 27]), anakinra (4% [1 of 27]), and canakinumab (4% [1 of 27]). For those patients without DS, other biologics used were infliximab (10% [11 of 115]), tocilizumab (9%

Table 2. Outcome measures at diagnosis and last recorded visit for patients with and without Down syndrome (DS)*

Arthritis and outcome measures	At baseline visit			At last visit		
	With DS	Without DS	*P*	With DS	Without DS	*P*
Physician global assessment of disease activity†	2.7 ± 2.6	2.5 ± 2.4	0.74	1.2 ± 1.4	1.0 ± 1.8	0.06
Patient/parent global assessment of overall well-being‡	4.0 ± 3.2	2.0 ± 2.4	<0.01#	2.3 ± 2.5	1.3 ± 1.7	0.03#
Joints with active arthritis	4.4 ± 7.0	4.0 ± 6.5	0.99	2.9 ± 5.6	0.8 ± 2.0	<0.01#
Joints with limited range of motion	4.3 ± 6.3	2.5 ± 4.2	0.32	3.3 ± 5.5	0.8 ± 2.0	<0.01#
Childhood Health Assessment Questionnaire§	1.2 ± 0.8	0.4 ± 0.5	<0.01#	1.1 ± 0.7	0.2 ± 0.5	<0.01#
Clinical Juvenile Arthritis Disease Activity Score 10¶	6.1 ± 5.6	7.2 ± 7.2	0.91	4.4 ± 4.5	2.6 ± 4.5	<0.01#

* Values are the mean ± SD unless indicated otherwise.
† Scored on a 10-point Likert scale, where 0 = clinically inactive disease.
‡ Scored on a 10-point Likert scale, where 0 = very good.
§ Includes 8 domains; questionnaire scores were averaged to obtain disability index score (0–3), where 0 = no disability.
¶ The Clinical Juvenile Arthritis Disease Activity Score 10 comprises composite disease activity (0–30), which is the sum of the physician global assessment (on a 10-point Likert scale), patient/parent global assessment (on a 10-point Likert scale), and number of joints with active arthritis, capped at a maximum of 10, where ≤1.0 = inactive disease.
# Significant.

[10 of 115]), and abatacept (7% [8 of 115]), while tofacitinib, anakinra, canakinumab, golimumab, secukinumab, and certolizumab were used less frequently. At the last visit, 70% (25 of 36) of patients with DS and 55% (91 of 165) of those without DS were receiving biologic therapy, with most being treated with adalimumab (9 of 27 of those with DS and 45 of 91 of those without DS).

Outcome measures. At the baseline visit, there was only a significant difference ($P < 0.05$) between patients with DS and those without DS for patient/parent global assessment and C-HAQ scores. There was no significant difference between physician global assessment, joints with active arthritis, joints with limited ROM, or cJADAS-10 scores between groups. At the last recorded visit, there was a significant difference ($P < 0.05$) for all outcome measures except for physician global assessment ($P = 0.06$) (Table 2). There was also more disease activity (based on the cJADAS-10) seen in patients with DS compared to those without DS between baseline visits and the last recorded visits (Table 3).

DISCUSSION

Similar to previous reports (4,5), most patients with DA in the nCARRA registry presented with polyarticular, seronegative disease. There was no significant difference between the time to diagnosis for patients in the nCARRA registry cohort, and those with DA had shorter time to diagnosis (8.3 months) compared to previous reports

Table 3. Clinical Juvenile Arthritis Disease Activity Score (cJADAS-10) for patients with and without Down syndrome (DS)*

Disease subtype and activity†	At baseline visit		At last visit	
	With DS	Without DS	With DS	Without DS
Oligoarticular disease‡				
Inactive disease (≤1.0)	–	1	2	8
Low disease activity (>1.0 to <1.5)	–	–	–	–
Moderate disease activity (1.51 to 4.0)	–	2	2	2
High disease activity (>4.0)	3	11	–	4
Polyarticular disease§				
Inactive disease (≤1.0)	5	30	7	71
Low disease activity (>1.0 to ≤2.5)	3	12	6	13
Moderate disease activity (2.51 to 8.5)	8	26	6	23
High disease activity (>8.5)	8	47	6	8

* The cJADAS-10 comprises composite disease activity score (0–30), which is the sum of the physician global assessment (on a 10-point Likert scale), patient/parent global assessment (on a 10-point Likert scale), and number of joints with active arthritis, capped at a maximum of 10, where ≤1.0 = inactive disease.
† Systemic, psoriatic, enthesitis-related, and undifferentiated subtypes of arthritis not included.
‡ At the baseline visit, the total number of patients with DS with oligoarticular disease = 3, and the total number of patients without DS with oligoarticular disease = 14. At the last visit, the total number of patients with DS with oligoarticular disease = 4, and the total number of patients without DS with oligoarticular disease = 14.
§ At the baseline visit, the total number of patients with DS with polyarticular disease = 24, and the total number of patients without DS with polyarticular disease = 115. At the last visit, the total number of patients with DS with polyarticular disease = 25, and the total number of patients without DS with polyarticular disease = 115.

of a 2–3-year average from symptom onset to diagnosis (4,5). Despite a shorter time to diagnosis compared to historical cohorts, patients with DA in the nCARRA registry had similar findings of bony joint damage on imaging at presentation (38%) compared to previous reports of 30–42% in patients with DA (4,5). This is also a higher frequency of bony joint damage compared to those with JIA (22%) in the nCARRA registry, which may suggest that DA is a more aggressive, destructive disease compared to JIA. However, one-third of patients with and without DS in the nCARRA registry did not have imaging at diagnosis, so it is unclear if more patients would have had abnormal imaging if it were completed at diagnosis. Larger prospective studies are needed to assess the relationship between time to diagnosis, bony changes, and joint outcomes in DA.

Dissimilar to previous reports of DA, morning stiffness was present in less than half (45%) of the patients with DA in the present study (which was similar for those with JIA [51%]) and many patients (44%) had normal laboratory tests at diagnosis in the nCARRA registry. These findings complicate screening and evaluation for DA and support the need for novel screening tools for children with DS. We have advocated for education of families and medical providers of children with DS to increase awareness of DA (5), but there is need for routine musculoskeletal screening that is pertinent to children with DS. This could be in line with other comorbidity screening that takes place on a regular basis for children with DS, such as annual thyroid screening (11).

The cohort of patients with DA in the present study had less disease burden, and their illness was identified sooner and treated more aggressively with earlier initiation of DMARD and biologic therapy compared to a previous report of patients with DA (5). However, when compared to baseline assessments of those with JIA without DS in the nCARRA registry, there was no significant difference ($P < 0.05$) in physician global assessment, joints with active arthritis and limited ROM, and cJADAS-10 score (Tables 2 and 3). There was a significant difference ($P < 0.05$) in patient/parent global assessment and C-HAQ score. This significant difference could be due to decreased overall well-being because of other complications associated with DS. Additionally, the C-HAQ may not be the best outcome measure of physical function for children with DS as it assumes neurotypical appropriate development, which can vary widely in children with DS. This assumption of development may also explain why there was little change in the average C-HAQ score between diagnosis and the last visit. Moreover, at the last recorded visit, JIA patients without DS had less disease burden, with a significant difference ($P < 0.05$) in joints with active arthritis, limited ROM, and cJADAS-10 score (Tables 2 and 3). This finding suggests that, despite a similar clinical presentation at baseline and a similar approach to therapy, patients with DA have higher disease burden than those with JIA. This higher disease burden further reinforces the need to determine the most effective and optimal therapy for those with DA, which has yet to be determined, and may be different compared to those with JIA.

Over the course of treatment, the therapy in 93% of the patients with DA and 25% of the patients with JIA who were taking methotrexate was discontinued due to adverse events. It is well described that children with DS have increased toxicity with methotrexate, but lower doses may be tolerated and still effective (12). This finding may indicate that methotrexate is effective at treating arthritis in some patients with DA; additionally, it may also represent providers' use of combination DMARD and biologic therapy due to increased disease severity. More work is needed to determine the ideal dose and administration of methotrexate or the safety and effectiveness of other traditional DMARDs in DA.

Biologic therapy was used in a similar percentage of patients with DA and JIA; however, 60% of patients with DA and 17% of patients with JIA had at least 1 change in biologic therapy due to ineffectiveness. The increase in adverse events with methotrexate therapy and the ineffectiveness of biologic therapy for children with DA creates a challenge of determining the ideal and most effective therapy. Medication challenges are commonly seen in children with DS, as there seems to be some variability in the pharmacokinetics of medications when administered to children with DS (13). There is evidence that children with DS have higher levels of proinflammatory cytokines, such as monocyte chemotactic protein 1, interleukin-6 (IL-6), IL-22, and tumor necrosis factor, suggesting that increased interferon signature is likely caused by trisomy 21 (14), which could benefit from biologic therapies that target JAK inhibition.

Limitations to the present study include small sample size and retrospective design, which precludes more sophisticated data analysis. The present study is a large national cohort study, and the findings substantiate previous reports of patients with DA. This may be an underestimate, as there are potentially more cases of DA that have not presented to a rheumatology clinic. Future studies in a larger population will allow for more detailed characterization of this condition and exploration of ideal therapy and outcome variables.

The present study reveals that children with DA have a similar presentation to children with JIA without DS; however, the disease course and disease burden of children with DA is significantly worse despite a similar treatment approach. This difference is due to more drug adverse events and higher rates of therapeutic ineffectiveness. Collective work to better characterize DA and to understand the pathophysiology and unique pharmacologic factors of the disease will help identify the most effective and tolerated therapies to treat arthritis in children with DS.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Jones had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Jones, Smith, Becker, Lovell.
Acquisition of data. Jones, Smith.
Analysis and interpretation of data. Jones, Becker, Lovell.

REFERENCES

1. De Graaf G, Buckley F, Skotko BG. Estimates of the live births, natural losses, and elective terminations with Down syndrome in the United States. Am J Med Genet A 2015;167A:756–67.
2. Asim A, Kumar A, Muthuswamy S, Jain S, Agarwal S. "Down syndrome: an insight of the disease." J Biomed Sci 2015;22:41.
3. Shin M, Siffel C, Correa A. Survival of children with mosaic Down syndrome. Am J Med Genet A 2010;152A:800–1.
4. Foley CM, Deely DA, MacDermott EJ, Killeen OG. Arthropathy of Down syndrome: an under-diagnosed inflammatory joint disease that warrants a name change. RMD Open 2019;5:e000890.
5. Jones JT, Talib N, Lovell D, Becker ML. Clinical features and treatment of Down syndrome arthropathy: experience from two US tertiary hospitals. Paediatr Drugs 2019;21:33–9.
6. Foley C, MacDermott E, Killeen O. Clinical and radiological features of down's arthropathy. Pediatric Rheumatology 2014;12 Suppl 1:P30.
7. Beukelman T, Kimura Y, Ilowite NT, Mieszkalski K, Natter MD, Burrell G, et al. The new Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry: design, rationale, and characteristics of patients enrolled in the first 12 months. Pediatr Rheumatol Online J 2017;15:30.
8. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994;37:1761–9.
9. McErlane F, Beresford MW, Baildam EM, Chieng SE, Davidson JE, Foster HE, et al. Validity of a three-variable Juvenile Arthritis Disease Activity Score in children with new-onset juvenile idiopathic arthritis. Ann Rheum Dis 2013;72:1983–8.
10. Consolaro A, Negro G, Chiara Gallo M, Bracciolini G, Ferrari C, Schiappapietra B, et al. Defining criteria for disease activity states in nonsystemic juvenile idiopathic arthritis based on a three-variable juvenile arthritis disease activity score. Arthritis Care Res (Hoboken) 2014;66:1703–9.
11. Bull MJ, Committee on Genetics. Health supervision for children with Down syndrome. Pediatrics 2011;128:393–406.
12. Kroll M, Kaupat-Bleckmann K, Moricke A, Alten J, Schewe DM, Stanulla M, et al. Methotrexate-associated toxicity in children with Down syndrome and acute lymphoblastic leukemia during consolidation therapy with high dose methotrexate according to ALL-BFM treatment regimen. Haematologica 2020;105:1013–20.
13. Hefti E, Blanco JG. Pharmacotherapeutic considerations for individuals with Down syndrome. Pharmacotherapy 2017;37:214–20.
14. Sullivan KD, Evans D, Pandey A, Hraha TH, Smith KP, Markham N, et al. Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation. Sci Rep 2017;7:14818.

APPENDIX A: CARRA REGISTRY SITE PRINCIPAL INVESTIGATORS, SUBINVESTIGATORS, AND RESEARCH COORDINATORS

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REVIEW

Guidance for Implementing Best Practice Therapeutic Exercise for Patients With Knee and Hip Osteoarthritis: What Does the Current Evidence Base Tell Us?

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Therapeutic exercise is a recommended first-line treatment for patients with knee and hip osteoarthritis (OA); however, there is little specific advice or practical resources to guide clinicians in its implementation. As the first in a series of projects by the Osteoarthritis Research Society International Rehabilitation Discussion Group to address this gap, we aim in this narrative review to synthesize current literature informing the implementation of therapeutic exercise for patients with knee and hip OA, focusing on evidence from systematic reviews and randomized controlled trials. Therapeutic exercise is safe for patients with knee and hip OA. Numerous types of therapeutic exercise (including aerobic, strengthening, neuromuscular, mind-body exercise) may be utilized at varying doses and in different settings to improve pain and function. Benefits from therapeutic exercise appear greater when dosage recommendations from general exercise guidelines for healthy adults are met. However, interim therapeutic exercise goals may also be useful, given that many barriers to achieving these dosages exist among this patient group. Theoretically-informed strategies to improve adherence to therapeutic exercise, such as patient education, goal-setting, monitoring, and feedback, may help maintain participation and optimize clinical benefits over the longer term. Sedentary behavior is also a risk factor for disability and lower quality of life in patients with knee and hip OA, although limited evidence exists regarding how best to reduce this behavior. Current evidence can be used to inform how to implement best practice therapeutic exercise at a sufficient and appropriate dose for patients with knee and hip OA.

Introduction

Osteoarthritis (OA), particularly of the knee and hip, is a common painful condition that imposes a substantial burden on individuals, health care systems, and society (1). Clinical guidelines recommend therapeutic exercise for the management of OA (1) irrespective of patient age, radiographic disease severity, pain intensity, functional levels, and comorbidities (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24434/abstract). The World Health Organization defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure (2). Exercise is a subcategory of physical activity that is planned, structured, and repetitive and can be

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referred to as therapeutic exercise when designed and prescribed by clinicians to achieve specific therapeutic goals. Therapeutic exercise provides multiple health benefits to patients with knee and hip OA including effects on pain, functional disability, quality of life, and emotional well-being (3,4). It can delay the need for joint replacement surgery (5), as well as have more general health benefits, including reducing the risk of comorbidities such as ischemic heart disease, diabetes mellitus, and stroke (6) and contributing to weight maintenance and weight loss (7). There is also some evidence that therapeutic exercise programs are cost effective (8). However, the description of therapeutic exercise programs within most clinical trials has insufficient detail to allow replication in clinical practice (9), and there is little specific advice or practical resources provided within clinical guidelines about how to implement best practice therapeutic exercise effectively (10). As the first in a series of projects designed to address this gap by the Osteoarthritis Research Society International (OARSI) Rehabilitation Discussion Group, we aimed to synthesize current literature (focusing on systematic reviews and randomized controlled trials) relating to therapeutic exercise for patients with knee and hip OA.

What type of therapeutic exercise should be undertaken by patients with knee and hip OA?

Systematic reviews suggest that benefits can be gained from many types of therapeutic exercise including, but not limited to, aerobic exercise, strength training, neuromuscular exercise, and mind-body exercise such as Tai Chi and yoga (3,4). Randomized controlled trials (RCTs) of aerobic exercise for patients with knee and hip OA (aimed at improving cardiorespiratory fitness [11]) largely focus on walking but also include cycling (e.g., stationary bike) (3,4). Walking is often an ideal choice of therapeutic exercise given its accessibility and the variety of surfaces (treadmill, indoors, outdoors), structures (independent versus supervised group programs), and types of walking available (e.g., Nordic walking).

Strength training is recommended to combat age-related sarcopenia and muscle weakness commonly associated with knee and hip OA (11). Strength training commonly targets the major lower extremity muscle groups appropriate for the affected joint according to individual impairments (e.g., hip flexors, extensors, abductors, adductors and rotators; knee flexors and extensors) (3,4). Based on the individual's ability and access to equipment, resistance can be applied using body weight, resistance bands, free weights and weight machines, as similar benefits for pain and function occur with different forms of strength training (12). Neuromuscular exercise can be used to improve sensorimotor control, proprioception, balance, and functional movement (11). There is strong evidence for the role of balance exercise in reducing falls in older adults (13), making its inclusion in a therapeutic exercise program logical when an increased risk of falls is identified. Mind–body exercises such as Tai Chi and yoga are gaining popularity and have been recommended for some patients in recent OA clinical guidelines (14), although the evidence is still relatively limited, particularly for yoga (15).

The magnitudes of benefits for pain and function from therapeutic exercise are generally small to moderate, which are similar or better than those of commonly used pain-relieving drugs (14). However, few studies have directly compared the effects of different types of therapeutic exercise. While there is indirect evidence suggesting that the benefits may vary according to type and combination of exercise, there is a lack of agreement as to which type or combination is most beneficial. A network meta-analysis by Uthman et al (3) concluded that a combined approach to increase strength, flexibility, and aerobic capacity was most likely to be effective for lower extremity OA, whereas a meta-regression analysis by Juhl et al (4) concluded that single-type exercise programs (either aerobic, resistance, or performance exercise) were more effective than programs that included different types of exercise. Both land- and water-based therapeutic exercise programs give comparable positive results for pain and function (16). Water-based exercise (or hydrotherapy) has the additional benefit of buoyancy and decreased joint impact, and may be preferable for some, such as those with more advanced disease or when land-based exercise is too painful (14).

What dosage should be used?

Currently there is limited evidence regarding the optimal dosage, including intensity, of therapeutic exercise needed for clinical benefits in patients with knee and hip OA. While it appears that benefits can be derived from both lower and higher intensity therapeutic exercise (17), there does seem to be some suggestion that benefits may be larger when sufficient and appropriate doses are undertaken. A meta-analysis by Moseng et al (18) showed that land-based supervised therapeutic exercise in patients with hip OA significantly reduced pain only when exercise doses met the American College of Sports Medicine (ACSM) general exercise recommendations for healthy adults for cardiorespiratory fitness, muscular strength, and flexibility (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24434/abstract) (11).

In knee OA, a meta-analysis showed that exercise interventions following the ACSM criteria for strength training (performed with an external load >40% of 1 repetition maximum, in 2–4 sets of 8–12 repetitions, in at least 2–3 sessions per week [11,19]) provided superior outcomes in knee extensor strength but not in pain or disability (19). While dosages recommended in general exercise guidelines for healthy adults therefore appear appropriate for patients with knee and hip OA (10), interim therapeutic exercise goals may also be useful given that many barriers to achieving these dosages can exist among this patient group. For example, an interim target for aerobic exercise could be to obtain at least

45 minutes/week of moderate-to-vigorous exercise, as this dosage has been associated with maintaining or improving to a high level of physical function in individuals with knee OA (20). While walking 10,000 steps/day is commonly cited as a general fitness-related step goal (21), walking 6,000 steps/day has been found to be a preliminary step goal that protects against the development of functional limitation in knee OA (22) and could therefore be an additional useful interim target in patients with knee and hip OA.

How should a therapeutic exercise program be progressed or modified?

General exercise guidelines for healthy adults recommend that to achieve and maintain a sufficient dose, exercise frequency, duration, and intensity should be progressed gradually over time, beginning first with duration, followed by frequency, and finally intensity (23). Within RCTs of therapeutic exercise for patients with knee and hip OA, information about how exercise programs are tailored and progressed is often lacking, making replication within clinical practice difficult (9). Strengthening exercise can be progressed via serial testing of maximal muscle strength to progress the resistance applied (e.g., % of true or estimated 1-repetition maximum) (11). An alternate approach for progression is to select the resistance that makes the last repetition in a set difficult to complete (e.g., 8 of 10 difficulty, where 0 = no effort, and 10 = hardest effort you can give) (11). Similarly, aerobic exercise can be progressed to achieve target heart rates (based on individual capacity) measured during exercise bouts (11). An alternate approach is the use of subjective reports of perceived exertion, such as the Borg Rating of Perceived Exertion Scale (24). Wearable devices such as accelerometers and pedometers or daily exercise logs may also be used to monitor and advance therapeutic exercise programs (25).

Some patients with knee and hip OA report discomfort or pain during exercise, but the size of acute activity-induced pain flares has been found to decrease with an increasing number of therapeutic exercise sessions (26). However, the role of pain in informing decisions about dosage and progression of therapeutic exercise for patients with knee and hip OA remains unclear. A systematic review including data from 7 RCTs and 385 participants with chronic musculoskeletal conditions found that exercising into pain resulted in a small but significantly greater benefit for pain reduction in the short term than pain-free exercise. However, in the medium and long term, there was no clear superiority of one treatment over another (27). In reality, modification of the therapeutic exercise program may be necessary if pain levels are unacceptable to the patient, which could include changes to the type, intensity, duration, or frequency of the program.

Both self-reported and performance-based outcome measures have been used to assess the effects of therapeutic exercise programs in patients with knee and hip OA, and these outcomes may inform progression or modification of therapeutic exercise programs. The timeframe for reassessment varies, but generally studies have used intervals of 8–12 weeks (3,4), often corresponding to the length of the intervention program. Similar time frames may therefore be useful reassessment points within clinical practice. A number of organizations have developed recommendations around core domains of measurement for patients with OA. The International Consortium for Health Outcomes Measurement (ICHOM) defines a minimum standard set of outcome measures for hip and knee OA (28), with a focus on those outcomes that matter most to patients, including pain, physical functioning, and health-related quality of life. Physical performance measures have also been used to determine if the objectives of the therapeutic exercise program are being achieved, such as increases in muscle strength, joint mobility, or other functional improvements. The OARSI recommended a core set of physical performance measures for use in patients with hip and knee OA (29). This comprises the 30-second chair stand test, 40-meter fast-paced walk test, and a stair climb test, with additional tests including the timed up and go and the 6-minute walk test.

How can therapeutic exercise programs be delivered?

A variety of delivery modes can be utilized for therapeutic exercise programs including individual (one-on-one), class-based (group), home-based, or a combination. Systematic reviews have demonstrated similar benefits in terms of pain and function across different delivery modes (14). Group programs supervised by health professionals have the advantages of incorporating social interaction, which may facilitate exercise adherence, and of lower cost delivery than individualized care.

Supervision, particularly in the initial stages of a class-based or home-based therapeutic exercise program, can help promote safe and correct exercise technique and ensure that the exercise dosage is appropriate for the patient's physical ability and program goals. In a systematic review, Juhl et al (4) found a significant relationship between the number of supervised sessions and the pain-relieving benefits of aerobic (but not resistance) exercise for patients with knee OA. Supervision may also be provided remotely using e-health technologies such as telehealth, mobile health, and movement sensors (e.g., wearable technology) (30). Qualitative research investigating patients' and clinicians' perceptions and experiences with remotely delivered interventions reports themes such as convenience, flexibility, and empowerment to self-manage, demonstrating that this delivery method is becoming more feasible and acceptable (31). Remote delivery may also allow for greater opportunity for patients to engage with exercise practitioners, especially in regional and remote areas.

How can therapeutic exercise programs be individualized?

Clinical outcomes from therapeutic programs vary between patients, and it is now recognized that programs should be individualized rather than use a one-size-fits-all approach (10,32). Although evidence to support individualization is scarce, there is current interest in examining whether certain patient characteristics moderate outcomes from exercise, and whether exercise that is targeted to patients in specific phenotypes or subgroups optimizes clinical effects. There is some evidence that the presence of greater muscle strength and more neutral knee joint alignment is associated with greater improvements following exercise focused on knee stabilization training and quadriceps strengthening, respectively (33). The presence of cardiac problems may also moderate the effects of exercise in patients with knee OA, but this needs further testing (33). A number of clinical and pain OA phenotypes have been identified, including patient and disease characteristics (e.g., pain sensitization and radiographic severity [34]), which may help in the individualization of future therapeutic exercise programs.

Given that research into targeted therapeutic exercise approaches is in its infancy, a biopsychosocial assessment incorporating the patient's values, needs, and preferences can facilitate individualization of therapeutic exercise programs (1,32). This could include utilization of the type of therapeutic exercise that the patient is most likely to initiate and maintain and selection of strategies to increase adherence depending on the patient's specific barriers and facilitators (see below). In line with clinical guidelines (32), comorbidities could also be considered given that ~2 of 3 patients with knee and hip OA have at least 1 other chronic condition, and that more comorbidities are associated with greater pain intensity, more painful body sites, and worse function and quality of life (35). Exercise is effective in treating many chronic conditions (6). Therefore, individualizing the therapeutic exercise program according to the patient's comorbidities may not only improve OA-related symptoms but also symptoms of other chronic conditions and their overall health.

Is therapeutic exercise safe for patients with knee and hip OA?

Therapeutic exercise is safe for patients with knee and hip OA, including those with advanced disease (36–38). A systematic review found that at the group level there was no evidence of serious adverse events, increases in pain, decreases in physical function, progression of structural OA on imaging, or increased risk of total knee replacement with low impact therapeutic exercise of varying intensities (36). Another systematic review found that low-to-moderate–intensity therapeutic exercise was not harmful for articular cartilage in patients with knee OA (37). Even in patients with end-stage knee OA, walking can be performed safely without exacerbating pain (38). Less research has focused on the safety of exercise in individuals with hip OA, but few minor events are reported from land-based exercise (36). While there has been debate about whether higher impact activity, such as running, is safe for those with preexisting OA, a large cohort study showed that self-selected running was associated with improved knee pain without worsening of structural disease progression over 48 months in patients age >50 years with knee OA (39).

Should sedentary behavior be targeted?

The current focus has been on promoting therapeutic exercise among patients with knee and hip OA, with little attention paid to reducing sedentary behavior (such as prolonged sitting). Recent observational studies suggest that independent of time spent in general physical activity, prolonged time in sedentary behavior is associated with increased risk of functional limitation, disability, and lower quality of life (40) in adults with knee OA. In addition, White et al (22) found that replacing 60 minutes of sedentary activity with 60 minutes of light-intensity physical activity was associated with a reduced risk of developing slow gait speed.

At present, the effect of therapeutic exercise programs in reducing sedentary behavior among patients with OA is unclear given a lack of robust research. Among general older adults, a meta-analysis found that interventions that specifically targeted reduced sitting time (such as sit–stand desks) were more effective in decreasing sedentary behavior than physical activity interventions alone (41). Clearly, further research is needed in this area to address sedentary behavior in patients with knee and hip OA, including, for example, whether interventions such as sit–stand desks are acceptable, tolerated, and effective among patients with joint pain.

What are the barriers and facilitators to patients with knee and hip OA initiating and adhering to therapeutic exercise?

The clinical benefits following a therapeutic exercise program decline over time (3,4) most likely due to lack of adherence. Maintaining a therapeutic exercise program over the long-term can be challenging. Engagement in therapeutic exercise among patients with knee and hip OA is influenced by a complex interplay between physical, personal (including psychologic), and social–environmental factors (42,43). A systematic review of qualitative evidence in knee and hip OA found that facilitators for therapeutic exercise included the following: aiming at symptom relief and mobility; positive exercise experiences and beliefs; knowledge; a "keep going" attitude; adjusting and prioritizing therapeutic exercise; and having health care professionals' and social support.

Barriers to therapeutic exercise included the following: pain and physical limitations; nonpositive therapeutic exercise

Table 1. Barriers and facilitators to therapeutic exercise for knee and hip osteoarthritis (OA) mapped to the Theoretical Domains Framework*

Domain	Example barrier	Example facilitator
Knowledge	Lack of disease knowledge/education	Having undertaken OA education class
Skills		Higher level of physical fitness
Social/professional identity	Self-perception of being inactive	Feeling of contributing to the study, which will benefit others long-term
Beliefs about capabilities	Beliefs about limitations due to disability	Low level of self-reported physical limitations
Optimism	Fatalism regarding knee OA	Positive exercise attitude
Beliefs about consequences	Beliefs about disease	Perceived benefits of exercising
Reinforcement	Lack of improvement with exercises	Previous positive personal experience of exercise
Intentions	Lack of motivation	Loyalty to physical therapist
Goals	Short-term goal setting only	Long-term and short-term goals
Memory, attention, and decision processes	Forgetfulness	Good quality sleep
Environmental context and resources	Use of a walking aid	Online program
Social influences	Family commitments	Low social strain
Emotion	Anxiety	Improved depression with exercise
Behavioral regulation		Doing exercise at own pace in own time

* See reference 43.

experiences, beliefs, and information; OA-related distress; a resigned attitude; and lack of motivation, behavioral regulation, professional support, and negative social comparison with co-exercisers (42). A scoping review mapped the barriers and facilitators to therapeutic exercise to the Theoretical Domains Framework (based on behavior change theory), as shown in Table 1 (43). The greatest number of unique barriers and facilitators mapped to the environmental context and resources domain (e.g., cost, accessibility, weather, and equipment). Additionally, many barriers were related to beliefs about the consequences of therapeutic exercise (43). This is supported by a recent qualitative study that found that once patients had been diagnosed with bone-on-bone changes, many disregarded therapeutic exercise programs, as they erroneously believed these would further damage their joints (44). These barriers and facilitators are important to consider when implementing strategies to increase adherence to therapeutic exercise for patients with knee and hip OA (discussed below).

What strategies and behavior change techniques can be used to increase patient adherence to therapeutic exercise?

Various strategies to improve adherence to therapeutic exercise have been explored among patients with knee and hip OA, but inconsistent results are often reported (45). This may partially be due to a lack of standardized or robust measure of exercise adherence (45).

Patient education is recommended as a core treatment for patients with knee and hip OA (1) and has been found to be an effective strategy to increase uptake of, and adherence to, therapeutic exercise (45). For example, education about the benefits of therapeutic exercise for OA, including its low risk of harmful effects, could be used to address false beliefs about the consequences of exercising with OA (43), pain could be explained as a modifiable symptom, and treatment focus could be shifted away from a structural damage model toward a person-centered approach that targets modifiable biopsychosocial factors influencing pain and disability (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24434/abstract).

A strong therapeutic alliance with the clinician during treatment can facilitate adherence to therapeutic exercise in patients with OA and can improve pain outcomes in patients with chronic musculoskeletal pain (46). Characteristics of the therapeutic alliance that are predictive of exercise adherence include agreement on goals and tasks, clear communication, a sense of connectedness, positive feedback, genuine interest, individualized care plans, trust in the clinician, and feeling empowered (47).

Behavior change theory can inform strategies to maximize exercise adherence. Five particular behavior change techniques can increase adherence to therapeutic exercise in patients with persistent musculoskeletal pain (48). These include goal setting, social support, instruction of behavior, demonstration of behavior, and practice/rehearsal. Feedback and monitoring interventions can also positively impact exercise adherence in older adults (45). Adults with OA believe that ongoing follow-up and review of progress, including supervision and correction of exercise technique, and longer term follow-up (>3 months after exercise commencement) for monitoring and progression of the exercise program are important for adherence (49). This belief is supported by evidence that booster sessions increase adherence to therapeutic exercise in patients with OA (45).

Technology-enhanced strategies including mobile applications, wearable activity monitors, and text messaging/email prompts have been shown to promote exercise adherence among adults with musculoskeletal problems and to promote positive physical activity behaviors in healthy adults. Meta-analyses suggest that these digital interventions increase total

physical activity, moderate-to-vigorous activity, daily step count, and energy expenditure (50). There is also evidence that web-based exercise programming systems can improve adherence to home exercises prescribed by a clinician for adults with musculoskeletal problems and, when delivered in conjunction with remote support, achieve better adherence than paper exercise handouts (51). Preliminary research suggests that these types of technology-enhanced, adherence-enhancing strategies would be feasible to use among patients with knee and hip OA (52).

As pain is a commonly cited barrier to therapeutic exercise among patients with knee and hip OA, it could be argued that pharmacologic pain treatments should be delivered alongside therapeutic exercise. However, there is conflicting evidence whether pain and function outcomes are improved when therapeutic exercise is combined with pharmacologic pain treatments (53). Further research in this area is therefore required.

Conclusions

Therapeutic exercise is beneficial and safe for patients with knee and hip OA, with no evidence of progression of structural OA, harm to articular cartilage, or increased risk of total knee replacement with therapeutic exercise of varying intensities. A range of therapeutic exercise types performed at higher and lower intensities and in different settings can improve pain and function in patients with knee and hip OA. Existing general exercise guidelines provide dosage recommendations for healthy individuals, and these are applicable for patients with knee and hip OA. However, interim goals may also be useful given that barriers to achieving these dosages exist in this patient population. A biopsychosocial approach can be used to individualize the therapeutic exercise program, aiming to achieve a sufficient dose to optimize outcomes. Theoretically informed strategies to improve adherence to therapeutic exercise may help maintain benefits over the longer term. Although limited evidence currently exists, it may be prudent also to specifically address sedentary behavior within clinical practice.

While this review has identified a plethora of RCTs, systematic reviews, and clinical guidelines that support the role of therapeutic exercise in the management of patients with knee and hip OA, it has also highlighted the lack of detail and clear direction about how to implement best practice therapeutic exercise in clinical practice. This limits the strength and specificity of any recommendations for clinical practice (9). Therapeutic exercise is a complex, multifaceted intervention. As reporting of therapeutic exercise in most RCTs lacks detail (about its dose, how it was individualized and progressed, where and by whom it was delivered, and what training was completed to undertake therapeutic exercise delivery), the ability to replicate exercise interventions is limited. This may result in suboptimal delivery of therapeutic exercise within clinical practice (54), reducing the potential benefit of exercise for patients.

To better support implementation of therapeutic exercise, researchers should fully report and describe therapeutic exercise programs tested within RCTs in accordance with best practice guidance and recommendations (55). We will use the findings from this narrative review to inform the development of position statements and practical resources to support clinicians to implement best practice therapeutic exercise for patients with knee and hip OA. Other areas for potential future research identified within this review include exploration of the following: the optimal dose of therapeutic exercise, including the role of pain in exercise progression; potential moderators of the effect of exercise; how to best measure and improve adherence to exercise; the effectiveness of interventions targeting sedentary behavior among individuals with knee and hip OA; and the effectiveness of pharmacologic pain treatments combined with therapeutic exercise among patients with knee and hip OA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication.

REFERENCES

1. Bannuru RR, Osani MC, Vaysbrot EE, Arden N, Bennell K, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019;27:1578–89.
2. World Health Organization. Global recommendations on physical activity for health. January 2010. URL: https://www.who.int/publications/i/item/9789241599979.
3. Uthman OA, van der Windt DA, Jordan JL, Dziedzic KS, Healey EL, Peat GM, et al. Exercise for lower limb osteoarthritis: systematic review incorporating trial sequential analysis and network meta-analysis. BMJ 2013;347:f5555.
4. Juhl C, Christensen R, Roos EM, Zhang W, Lund H. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. Arthritis Rheumatol 2014;66:622–36.
5. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Rasmussen S, et al. Total knee replacement and non-surgical treatment of knee osteoarthritis: 2-year outcome from two parallel randomized controlled trials. Osteoarthritis Cartilage 2018;26:1170–80.
6. Pedersen BK, Saltin B. Exercise as medicine: evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports 2015;S3:1–72.
7. Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA 2013;310:1263–73.
8. Abbott JH, Wilson R, Pinto D, Chapple CM, Wright AA, MOA Trial Team. Incremental clinical effectiveness and cost effectiveness of providing supervised physiotherapy in addition to usual medical care in patients with osteoarthritis of the hip or knee: 2-year results of the MOA randomised controlled trial. Osteoarthritis Cartilage 2019;27:424–34.

9. Bartholdy C, Nielsen SM, Warming S, Hunter DJ, Christensen R, Henriksen M. Poor replicability of recommended exercise interventions for knee osteoarthritis: a descriptive analysis of evidence informing current guidelines and recommendations. Osteoarthritis Cartilage 2019;27:3–22.
10. Rausch Osthoff AK, Niedermann K, Braun J, Adams J, Brodin N, Dagfinrud H, et al. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis 2018;77:1251–60.
11. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334–59.
12. Fransen M, McConnell S, Harmer AR, van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2015;1:CD004376.
13. Sherrington C, Fairhall NJ, Wallbank GK, Tiedemann A, Michaleff ZA, Howard K, et al. Exercise for preventing falls in older people living in the community. Cochrane Database of Syst Rev 2019:CD012424.
14. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheumatol 2020;72:220–33.
15. Lauche R, Hunter DJ, Adams J, Cramer H. Yoga for osteoarthritis: a systematic review and meta-analysis. Curr Rheumatol Rep 2019;21:47.
16. Dong R, Wu Y, Xu S, Zhang L, Ying J, Jin H, et al. Is aquatic exercise more effective than land-based exercise for knee osteoarthritis? Medicine (Baltimore) 2018;97:e13823.
17. Regnaux JP, Lefevre-Colau MM, Trinquart L, Nguyen C, Boutron I, Brosseau L, et al. High-intensity versus low-intensity physical activity or exercise in people with hip or knee osteoarthritis. Cochrane Database Syst Rev 2015:CD010203.
18. Moseng T, Dagfinrud H, Smedslund G, Osteras N. The importance of dose in land-based supervised exercise for people with hip osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2017;25:1563–76.
19. Bartholdy C, Juhl C, Christensen R, Lund H, Zhang W, Henriksen M. The role of muscle strengthening in exercise therapy for knee osteoarthritis: a systematic review and meta-regression analysis of randomized trials. Semin Arthritis Rheum 2017;47:9–21.
20. Dunlop DD, Song J, Lee J, Gilbert AL, Semanik PA, Ehrlich-Jones L, et al. Physical activity minimum threshold predicting improved function in adults with lower-extremity symptoms. Arthritis Care Res (Hoboken) 2017;69:475–83.
21. Tudor-Locke C, Hatano Y, Pangrazi RP, Kang M. Revisiting, "how many steps are enough?" Med Sci Sports Exerc 2008;40:S537–43.
22. White DK, Tudor-Locke C, Zhang Y, Fielding R, LaValley M, Felson DT, et al. Daily walking and the risk of incident functional limitation in knee osteoarthritis: an observational study. Arthritis Care Res (Hoboken) 2014;66:1328–36.
23. US Department of Health and Human Services. Physical activity guidelines for Americans. 2018. URL: https://health.gov/our-work/physical-activity.
24. Borg G. Borg's perceived exertion and pain scales. Champaign (IL): Human Kinetics; 1998.
25. Sliepen M, Brandes M, Rosenbaum D. Current physical activity monitors in hip and knee osteoarthritis: a review [review]. Arthritis Care Res (Hoboken) 2017;69:1460–6.
26. Sandal LF, Roos EM, Bogesvang SJ, Thorlund JB. Pain trajectory and exercise-induced pain flares during 8 weeks of neuromuscular exercise in individuals with knee and hip pain. Osteoarthritis Cartilage 2016;24:589–92.
27. Smith BE, Hendrick P, Smith TO, Bateman M, Moffatt F, Rathleff MS, et al. Should exercises be painful in the management of chronic musculoskeletal pain? A systematic review and meta-analysis. Br J Sports Med 2017;51:1679–87.
28. International Consortium for Health Outcomes Measurement. Hip and knee osteoarthritis data collection reference guide. URL: https://ichom.org/files/medical-conditions/hip-knee-osteoarthritis/hip-knee-osteoarthritis-reference-guide.pdf.
29. Dobson F, Hinman RS, Roos EM, Abbott JH, Stratford P, Davis AM, et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. Osteoarthritis Cartilage 2013;21:1042–52.
30. Schafer AG, Zalpour C, von Piekartz H, Hall TM, Paelke V. The efficacy of electronic health-supported home exercise interventions for patients with osteoarthritis of the knee: systematic review. J Med Internet Res 2018;20:e152.
31. Lawford BJ, Delany C, Bennell KL, Hinman RS. "I was really pleasantly surprised": firsthand experience and shifts in physical therapist perceptions of telephone-delivered exercise therapy for knee osteoarthritis–a qualitative study. Arthritis Care Res (Hoboken) 2019;71:545–57.
32. Fernandes L, Hagen KB, Bijlsma JW, Andreassen O, Christensen P, Conaghan PG, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 2013;72:1125–35.
33. Quicke JG, Runhaar J, van der Windt DA, Healey EL, Foster NE, Holden MA. Moderators of the effects of therapeutic exercise for people with knee and hip osteoarthritis: a systematic review of subgroup analyses from randomised controlled trials. Osteoarthr Cartil Open 2020;2:100113.
34. Deveza LA, Melo L, Yamato TP, Mills K, Ravi V, Hunter DJ. Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. Osteoarthritis Cartilage 2017;25:1926–41.
35. Wesseling J, Welsing PM, Bierma-Zeinstra SM, Dekker J, Gorter KJ, Kloppenburg M, et al. Impact of self-reported comorbidity on physical and mental health status in early symptomatic osteoarthritis: the CHECK (Cohort Hip and Cohort Knee) study. Rheumatology (Oxford) 2013;52:180–8.
36. Quicke J, Foster N, Thomas M, Holden M. Is long-term physical activity safe for older adults with knee pain? A systematic review. Osteoarthritis Cartilage 2015;23:1445–56.
37. Bricca A, Juhl CB, Steultjens M, Wirth W, Roos EM. Impact of exercise on articular cartilage in people at risk of, or with established, knee osteoarthritis: a systematic review of randomised controlled trials. Br J Sports Med 2019;53:940–7.
38. Wallis JA, Webster KE, Levinger P, Singh PJ, Fong C, Taylor NF. A walking program for people with severe knee osteoarthritis did not reduce pain but may have benefits for cardiovascular health: a phase II randomised controlled trial. Osteoarthritis Cartilage 2017;25:1969–79.
39. Lo GH, Musa SM, Driban JB, Kriska AM, McAlindon TE, Souza RB, et al. Running does not increase symptoms or structural progression in people with knee osteoarthritis: data from the osteoarthritis initiative. Clin Rheumatol 2018;37:2497–504.
40. Pinto D, Song J, Lee J, Chang RW, Semanik PA, Ehrlich-Jones LS, et al. Association between sedentary time and quality of life from the Osteoarthritis Initiative: who might benefit most from treatment? Arch Phys Med Rehabil 2017;98:2485–90.

41. Prince SA, Saunders TJ, Gresty K, Reid RD. A comparison of the effectiveness of physical activity and sedentary behaviour interventions in reducing sedentary time in adults: a systematic review and meta-analysis of controlled trials. Obes Rev 2014;15:905–19.
42. Kanavaki AM, Rushton A, Efstathiou N, Alrushud A, Klocke R, Abhishek A, et al. Barriers and facilitators of physical activity in knee and hip osteoarthritis: a systematic review of qualitative evidence. BMJ Open 2017;7:e017042.
43. Dobson F, Bennell K, French S, Nicolson PJA, Klassman R, Holden M, et al. Barriers and facilitators to exercise participation in people with hip and/or knee osteoarthritis: synthesis of the literature using behaviour change theory. Am J Phys Med Rehabil 2016;95:372–89.
44. Bunzli S, O'Brien P, Ayton D, Dowsey M, Gunn J, Choong P, et al. Misconceptions and the acceptance of evidence-based nonsurgical interventions for knee osteoarthritis: a qualitative study. Clin Orthop Relat Res 2019;477:1975–83.
45. Jordan JL, Holden MA, Mason E, Foster NE. Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev 2010 2010:CD005956.
46. Kinney M, Seider J, Beaty AF, Coughlin K, Dyal M, Clewley D. The impact of therapeutic alliance in physical therapy for chronic musculoskeletal pain: a systematic review of the literature. Physiother Theory Pract 2018:1–13.
47. Babatunde F, MacDermid J, MacIntyre N. Characteristics of therapeutic alliance in musculoskeletal physiotherapy and occupational therapy practice: a scoping review of the literature. BMC Health Serv Res 2017;17:375.
48. Meade LB, Bearne LM, Sweeney LH, Alageel SH, Godfrey EL. Behaviour change techniques associated with adherence to prescribed exercise in patients with persistent musculoskeletal pain: systematic review. Br J Health Psychol 2019;24:10–30.
49. Nicolson PJ, Hinman RS, French SD, Lonsdale C, Bennell KL. Improving adherence to exercise: do people with knee osteoarthritis and physical therapists agree on the behavioural approaches likely to succeed? Arthritis Care Res (Hoboken) 2018;70:388–97.
50. Stockwell S, Schofield P, Fisher A, Firth J, Jackson SE, Stubbs B, et al. Digital behavior change interventions to promote physical activity and/or reduce sedentary behavior in older adults: a systematic review and meta-analysis. Exp Gerontol 2019;120:68–87.
51. Bennell KL, Marshall CJ, Dobson F, Kasza J, Lonsdale C, Hinman RS. Does a web-based exercise programming system improve home exercise adherence for people with musculoskeletal conditions? A randomized controlled trial. Am J Phys Med Rehabil 2019;98:850–8.
52. Li LC, Sayre EC, Xie H, Clayton C, Feehan LM. A community-based physical activity counselling program for people with knee osteoarthritis: feasibility and preliminary efficacy of the track-OA study. JMIR Mhealth Uhealth 2017;5:e86.
53. Henriksen M, Christensen R, Klokker L, Bartholdy C, Bandak E, Ellegaard K, et al. Evaluation of the benefit of corticosteroid injection before exercise therapy in patients with osteoarthritis of the knee: a randomized clinical trial. JAMA Intern Med 2015;175:923–30.
54. Holden MA, Nicholls EE, Young J, Hay EM, Foster NE. Physical therapists' use of therapeutic exercise for patients with clinical knee osteoarthritis in the United Kingdom: in line with current recommendations? Physical Therapy 2008;88:1109–21.
55. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687.

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Limiting the Risk of Osteoarthritis After Anterior Cruciate Ligament Injury: Are Health Care Providers Missing the Opportunity to Intervene?

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Objective. To understand what sports orthopedic surgeons (OS), primary care physicians (PCPs) with sports medicine training, and physical therapists (PTs) managing nonelite athletes with anterior cruciate ligament (ACL) injury tell their patients about their osteoarthritis (OA) risk.

Methods. An electronic survey was distributed by the Canadian Academy of Sport and Exercise Medicine (PCPs, OS), the Sports and Orthopedic Divisions of the Canadian Physiotherapy Association (PTs), and to OS identified through the Royal College of Physicians and Surgeons and the Canadian Orthopaedic Association. The survey included 4 sections: demographics, factors discussed, timing of discussions, and discussion of risk factors and their management. Proportions or means with 95% confidence intervals were calculated.

Results. A total of 501 health care professionals (HCPs) responded (98 PCPs, 263 PTs, and 140 OS). Of those responding, 70–77% of physicians reported always discussing OA risk, but only 35% of PTs did. All HCPs reported that patient activities perceived as detrimental to knee health, ACL reinjury, and simultaneous injury to other structures in the knee were most often the reason for discussing OA risk. OA risk was discussed at initial management post-injury (65–94%), with few discussing risk subsequently. Eighty percent of physicians and 99% of PTs indicated that PTs were suited to provide OA risk and management information.

Conclusion. HCPs routinely managing people with ACL injury do not consistently discuss OA risk post-injury with them. Educational strategies for HCPs are urgently needed to develop care pathways inclusive of support for OA risk management following ACL injury.

INTRODUCTION

Posttraumatic osteoarthritis (OA) following knee injury is a significant problem in young adults. Snoeker et al reported a 6-fold increased hazard of diagnosed knee OA over 11 years in those with versus those without knee injury in people ages 25–34 years (1). Individuals with anterior cruciate ligament (ACL) tears were at highest risk. Surgical reconstruction of the ligament (ACLR), while restoring structural stability, does not prevent OA (2,3). Radiographic OA is present in 11.3%, 20.6%, and 51.6% at 5, 10, and 20 years, respectively, after ACLR (4). Other researchers report that up to 50% of people with ACL tears develop symptomatic OA within 8–15 years, irrespective of ACLR (5–9). Data from the Moon cohort indicate that up to 39% of patients seek health care for knee symptoms by 6 years after ACLR (10). This latter study was designed to determine the prevalence of significant knee pain and did not attempt to determine who met criteria for clinical or radiographic diagnosis of knee OA. Whether this early significant pain represents or is a precursor to early knee OA is unclear.

There is a pressing need to implement strategies that reduce the risk of symptomatic knee OA in those at high risk. However, current research and implementation priorities focus on primary

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SIGNIFICANCE & INNOVATIONS

- Health care professionals (HCPs), particularly physical therapists (PTs), who routinely manage people with anterior cruciate ligament (ACL) injury do not consistently discuss osteoarthritis (OA) risk with patients post-injury and during recovery.
- Greater than 80% of HCPs indicate that PTs are suited to have OA risk discussions, but only one-third of PTs report that they always have the discussion.
- There is a need and opportunity to limit the development and progression of symptomatic knee OA following ACL injury by incorporating education about OA risk factors and their management into post ACL injury care.

prevention of ACL injury (11) and surgical versus nonsurgical management of ACL tears (12,13), leaving a significant gap in research and care for those at risk of symptomatic OA. This gap is particularly concerning given the increasing rates of ACL injury (14,15).

There is limited research providing information regarding what individuals understand about their OA risk and whether they implement strategies to try to mitigate the risk. Research suggests that <5% of individuals perceive themselves to be at risk of OA post-injury (7,16) despite evidence showing that risk is ~50%. In a survey of 261 people who had ACLR 1–5 years previously, Bennell et al reported that 27% remembered discussing OA risk with any health care professional (HCP) (17). Of those who remembered a discussion (n = 62), only 25 could recall strategies for managing risk. What is not addressed in the literature is whether HCPs treating people with ACL injuries who are nonelite athletes discuss OA risk and recommend strategies to manage risk in an effort to limit the development of posttraumatic symptomatic knee OA.

We surveyed primary care sports physicians (PCPs), physical therapists (PTs), and sports orthopedic surgeons (OS) who routinely treat nonelite athletes with ACL injury to determine whether information on OA risk factors and management strategies is provided to people with ACL injury, what information is provided, when in the course of care the information is provided, and who do providers recommend should convey such information. Understanding whether and what HCPs communicate is a critical first step to determining what strategies are needed to develop and implement an intervention that can support patients with ACL injury for managing their risk factors for knee OA.

SUBJECTS AND METHODS

Study design and subjects. We conducted a cross-sectional survey of PTs, PCPs, and OS in Canada who treat people with ACL injuries. OS were identified through multiple sources: the Royal College of Physicians and Surgeons of Canada listing, which includes all physicians who are members of the College, limiting to those where we could identify ACL or arthroscopy practices based on internet searching; the OS listing from Scott's Directories (https://www.scottsdirectories.com/), a commercial entity compiling directories for businesses; and the Canadian Orthopaedic Association. Duplicates were removed and potential respondents were emailed, mailed, or faxed the survey from April to December 2017. Three reminders were sent after the initial invitation. PCPs were targeted through the Canadian Academy of Sports and Exercise Medicine (CASEM), and PTs were targeted through the Sports and Orthopaedic Divisions of the Canadian Physiotherapy Association (CPA). CASEM and the CPA distributed the survey to their membership from February to December 2017 and from May to December 2017, respectively, via e-blasts with 2 to 3 biweekly reminders after the initial invitation. In addition, a survey link was included in newsletters of CASEM and the CPA Sport Physiotherapy Division from March through May 2017.

Respondents were eligible if they were practicing in Canada and treated patients age ≥16 years who had ACL tears and were nonelite athletes. Elite athlete was defined as professional, second tier, or semiprofessional, including those competing at an international or national level, or who were in university and talent development programs (18). This work was approved by the Research Ethics Board, University Health Network (REB #16-6317). Completion and return of the survey were considered implied consent.

Data collected. We created a custom-designed survey that took ~10 minutes to complete. Content included practitioner eligibility criteria and the following sections.

Practitioner demographics. Information on demographics included male/female, province/territory of practice, years of experience (i.e., ≤3, >3 to 5, >5 to 10, >10 to 15, >15), and the number of patients with ACL injury treated per year (i.e., <10, 10–20, 21–50, 51–75, 76–100, >100).

Informing patients of OA risk. 1) Participants were asked about the frequency of discussion (never, sometimes, always); 2) those who responded "sometimes" or "always" to frequency of discussion had a list of factors (no/yes) influencing the discussion of OA risk, and branching response options for those who replied yes, with options including age (16–25, 26–35, >35 years); sex (male, female); body weight (normal, overweight, obese); activity level (excessive load physical activity, occupation involving heavy lifting, repetitive kneeling or stair climbing, low/limited physical activity, twisting/pivoting activities); type of acute injury management (conservative, surgical reconstruction); concurrent injury to another joint structure, e.g., meniscus, collateral ligament, chondral injury; revision ACLR; and other factors (open text); and 3) respondents were asked about specific risk factors discussed: knee reinjury; weight-gain; sedentary/limited physical activity; excessive physical activity; poor quadriceps, hamstrings, and core strength; poor flexibility; repetitive knee loading such as kneeling; squatting and heavy lifting and twisting activities; and other (open text).

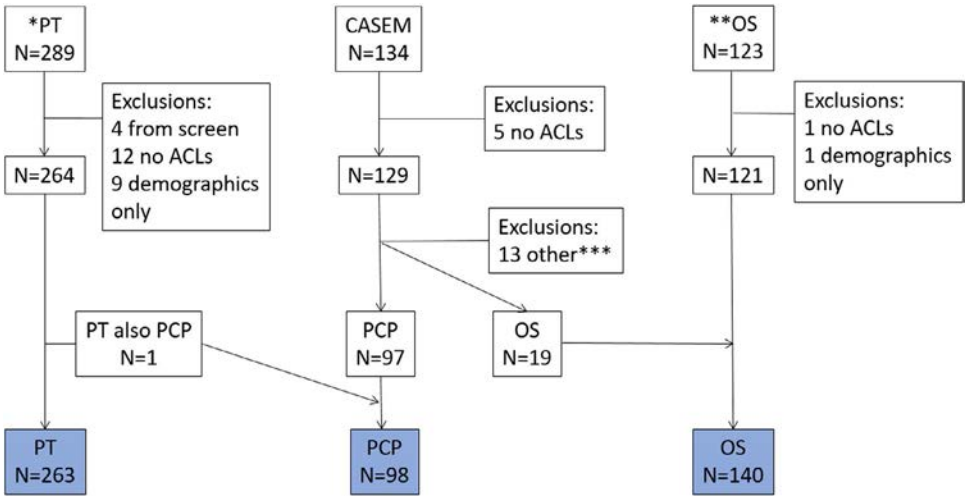

Figure 1. Flow diagram showing the respondents, with exclusions and consolidation by profession to derive the analytic sample: physical therapists (PTs), primary care sports physicians (PCPs), and orthopedic surgeons (OS). ACL = anterior cruciate ligament; CASEM = Canadian Academy of Sport and Exercise Medicine; * = members of the Canadian Physiotherapy Association Sports and Orthopaedic Divisions; ** = identified from the Royal College of Physicians and Surgeons of Canada, Scott's Directory, or the Canadian Orthopaedic Association; *** = "other" are physician members of CASEM but their area of practice could not be identified.

Timing of discussion. The timing of discussing OA risk factors included options of: discussion as part of the initial management post-injury, at 3–6 months post-injury, at >6 to 12 months post-injury, at >12 months post-injury, or no discussion of risk factors.

Type of advice. The survey also asked about advice (no/yes; and if yes, open text) and resources provided to patients about OA risk (no/yes; and if yes, open text), and asked for recommendations of which HCPs should discuss OA risk factors with patients (check all that apply: OS, PCP, rheumatologist, PT, kinesiologist, exercise physiologist, athletic therapist, other [open text]).

The first draft of the survey was designed by the study PI (AMD) who is a physical therapist and OA researcher trained in clinical epidemiology. Initial content was based on clinical knowledge of the trajectory of the care pathway for individuals with ACL injury, modifiable risk factors for knee OA from the published literature (19–22), and the evidence of therapeutic approaches to symptomatic knee OA that theoretically support management approaches addressing these risk factors (23–25). The draft survey was iteratively reviewed by members of the research team. The team included OS, PCPs, and PTs, all with expertise in managing individuals with ACL injury, a biomechanist with expertise in OA, and individuals who have experienced ACL injury. Their input resulted in revisions to clarify wording and some additional content. This revised version was reviewed by 2 additional clinicians for confirmation of clarity and content. The OS survey is provided online in Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24419/abstract. The survey content differed among HCPs only in that it specified their profession.

Statistical analysis. Data were analyzed separately by HCP discipline because these groups have a different expertise and because they assess and treat individuals at different times, with potentially different interventions over the course of ACL injury management. Descriptive statistics were calculated with means or proportions with 95% confidence intervals (95% CIs) calculated for continuous, nominal, and ordinal data.

RESULTS

Practitioner respondents. Details of the sampling, recruitment strategies, and respondent numbers resulting in the analytic sample are provided in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24419/abstract. In summary, of the 289 HCPs responding from the CPA Sports and Orthopaedic Divisions, there were 263 PTs with analyzable responses. We assumed that a PCP was unlikely to continue to practice as a PT and reassigned this individual as a PCP. There were 134 returned surveys from CASEM members. The 19 who identified themselves as an OS were reassigned to the OS group. CASEM members are all physicians, but because we were unable to determine their practice focus, we excluded the 13 declaring "other." A total of 123 OS returned the survey, with 121 providing analyzable responses. Realigning respondents by discipline, there were 140 OS, 98 PCPs, and 263 PTs who provided analyzable data (Figure 1).

The majority of OS were male, whereas approximately equal numbers of male and female PCPs responded (Table 1). Most PT respondents were female. The respondents were experienced, with most reporting >5 years experience and reporting that they treated >20 ACL patients per year. The

Table 1. Descriptive statistics of the health care providers (n = 501)*

	Primary care sports physician (n = 98)	Physical therapist (n = 263)	Orthopedic surgeon (n = 140)
Male	48 (49.0)	92 (35.0)	123 (87.9)
Experience, years			
≤5	18 (18.4)	66 (25.1)	24 (17.1)
>5 to 15	29 (29.6)	81 (30.8)	50 (35.7)
>15	51 (52.0)	116 (44.1)	66 (47.1)
ACLs treated per year			
≤20	44 (44.9)	228 (86.7)	25 (17.8)
21–50	30 (30.6)	26 (9.9)	42 (30.2)
>50	24 (24.5)	8 (3.0)	55 (39.3)
Missing	–	1 (0.4)	1 (0.7)
Practice location†			
West	39 (39.8)	121 (46.2)	67 (47.9)
Central	55 (56.1)	122 (46.9)	57 (40.7)
East	3 (3.1)	19 (7.2)	14 (10.0)
Missing	1 (1.0)	1 (0.4)	2 (1.4)

* Values are the number (%). ACLs = anterior cruciate ligaments.
† West includes Manitoba, Saskatchewan, Alberta, British Columbia, and the Territories (Northwest Territories, Nunavut, Yukon); central includes Ontario and Quebec; east includes New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador.

respondents generally were from across Canada. The largest proportion of respondents were from Ontario, British Columbia, and Alberta, followed by Quebec. Three PTs from the Territories responded, but there were no PCPs or OS respondents from the Territories. Additionally, there was no PCP respondent from New Brunswick.

Communicating the risk of OA. The majority of physicians indicated that they always inform their patients of their risk of knee OA; this number included 70 of 98 PCPs (71.4% [95% CI 61.8–79.4]) and 108 of 140 OS (77.1% [95% CI 69.5–83.3]). Eighty-nine of 263 PTs (33.8% [95% CI 28.4–39.8]) indicated that they always inform their patients. Most other respondents indicated that they sometimes discuss risk, with 1 PCP, 1 OS, and 24 PTs indicating that they never discuss OA risk.

Providers who inform their patients about OA risk also indicated which factors influence their decision to discuss OA risk (Table 2). Injury to another structure in the knee joint (71–88%) and a repeat ACL tear (63–81%) were the most common factors resulting in discussions of OA risk. Sixty-nine percent of PTs, 52% of PCPs, and 55% of OS indicated that activity level influences whether they inform their patients about OA risk. Of those, all providers indicated that excessive loading through activities and occupation, and activities requiring twisting and pivoting, were of concern. Limited physical activity was identified by 38%, 58%, and 34% of PCPs, PTs, and OS, respectively. Other factors were endorsed by <60% of the respondents in any provider group. Very few providers indicated that sex was a factor (4–16%), so that we could not determine whether male or female was influential. Age was not a factor, with a similar proportion of providers (72–89%)

Table 2. Proportion of providers reporting that patient, injury, and treatment factors influence informing patients of their osteoarthritis risk*

	Primary care physician (n = 97)	Physical therapist (n = 239)	Orthopedic surgeon (n = 139)
Age	35 (36.5); 27.5–46.4	116 (49.6); 43.2–55.9	72 (52.2); 43.9–60.3
Missing	1	5	1
Sex	4 (4.2); 1.6–10.0	14 (6.1); 3.7–10.0	22 (16.1); 10.9–23.1
Missing	1	10	2
Body weight	45 (46.9); 37.2–56.8	122 (53.5); 46.2–59.0	74 (53.6); 45.3–61.7
Missing	1	11	1
Activity level	50 (52.1); 42.2–61.8	151 (68.6); 62.2–74.4	76 (55.5); 47.1–63.9
Missing	1	19	2
Other joint injury	67 (71.3); 61.4–79.5	182 (83.5); 82.0–87.8	122 (88.4); 82.0–92.7
Missing	3	21	1
Repeat ACL injury	57 (63.3); 53.0–72.6	153 (71.8); 65.4–77.4	108 (80.6); 73.1–86.4
Missing	7	26	5
Acute injury management	33 (37.1); 27.8–47.5	79 (36.6); 30.4–43.2	63 (46.3); 38.2–54.7
Missing	8	23	3

* Values are the number (%); 95% confidence interval. Sample size is based on those who responded "sometimes" or "always" to informing their patients about osteoarthritis risk. ACL = anterior cruciate ligament.

Table 3. Osteoarthritis risk factors discussed with patients with ACL injury*

	Primary care physician (n = 97)		Physical therapist (n = 239)		Orthopedic surgeon (n = 139)	
	Sometimes	Always	Sometimes	Always	Sometimes	Always
Knee reinjury	32 (34.0); 25.3–44.1	60 (63.8); 53.8–72.8	76 (32.8); 27.0–39.0	146 (62.9); 56.6–68.9	32 (23.4); 17.1–31.1	102 (74.5); 66.6–81.0
Weight gain	37 (39.8); 30.4–49.9	48 (51.6); 41.6–61.5	124 (53.9); 47.5–60.2	70 (30.4); 24.9–36.7	57 (41.3); 33.4–49.6	62 (44.9); 36.9–53.3
Sedentary lifestyle	33 (35.9); 26.8–46.1	48 (52.2); 42.1–62.1	100 (42.9); 36.7–49.3	119 (51.1); 44.7–57.4	61 (46.9); 38.6–55.5	35 (26.9); 20.0–35.1
Excessive activity	42 (45.2); 35.4–55.3	37 (39.8); 30.4–49.9	103 (44.4); 38.3–44.6	90 (38.8); 32.8–45.2	60 (44.5); 36.3–53.6	53 (39.6); 31.3–48.4
Hamstring strength	36 (38.7); 29.5–48.9	40 (43.0); 33.4–53.2	75 (32.2); 26.5–38.4	127 (54.50); 48.1–61.0	54 (41.5); 33.4–50.5	27 (20.8); 14.7–28.5
Quadriceps strength	35 (37.6); 28.5–47.8	48 (51.6); 41.6–61.5	71 (30.6); 25.0–36.8	132 (56.9); 50.5–63.1	49 (38.0); 29.7–47.0	40 (31.0); 23.7–39.4
Core strength	40 (43.0); 33.4–53.2	29 (31.2); 22.7–41.2	95 (41.1); 35.0–47.6	83 (35.9); 30.0–42.3	45 (34.6); 27.0–43.1	26 (20.0); 14.0–27.7
Flexibility	42 (45.7); 35.9–55.8	22 (23.9); 16.4–33.6	100 (43.5); 37.2–49.9	85 (37.0); 31.0–43.4	53 (40.5); 32.4–49.0	17 (13.0); 8.3–19.8
Repetitive knee loading (squatting, etc.)	35 (37.6); 28.5–47.8	50 (53.8); 43.7–63.5	70 (51.1); 43.0–59.3	123 (53.0); 46.6–59.3	70 (51.1); 43.0–59.3	48 (35.0); 27.6–43.3

* Values are the number (%); 95% confidence interval. ACL = anterior cruciate ligament.

informing patients across the age spectrum. The exception was for PTs, where only 47% of the 116 (95% CI 38–56) who informed patients about risk reported doing so with patients age 16–25 years. Between 85% and 95% of providers informed patients who were overweight or obese about OA risk. Between 37% and 46% of HCPs indicated that type of management of the ACL injury influences informing patients about OA risk. Sixty-two percent of PCPs and PTs indicated that conservative management influences their decision. Conservative and surgical reconstruction each influence the decision for ~20% of OS, whereas 61% of OS indicated that both types of management are influential.

The majority of all HCPs indicated that they discuss knee reinjury as an OA risk factor; 60 of 88 PCPs (68%), 146 of 232 PTs (63%), and 102 of 137 OS (74%) reported that they always discuss reinjury (Table 3). Discussion of all other factors was much less frequent across all disciplines. Few respondents identified other potential risk factors. Joint alignment and biomechanics were most commonly identified as another factor, with 10 PTs and 12 OS indicating that they always discuss this factor.

Timing of discussion of OA risk factors. Eighty percent (95% CI 70–86) of PCPs and 94% (95% CI 89–97) of OS reported discussing OA risk as part of initial ACL injury management, whereas 65% (95% CI 58–71) of PTs reported discussing risk (Table 4). Discussions related to OA risk were reported less frequently after initial management, with 42% (95% CI 33–53) and 49% (95% CI 43–56) of PCPs and PTs, respectively, discussing risk at 3 to 6 months postsurgery. Only 13% (95% CI 8–20) of OS reported discussing risk during this period. Subsequently, through the first year post-injury, all HCPs reported less frequent discussion of OA risk.

Advice and resources provided. Approximately 75% (range 74–79%) of providers reported that they offer advice to help their patients manage OA risk. Combining the text responses of similar content for those who responded that they provide advice, the most commonly reported recommendations for the 66 PCP, 175 PT, and 102 OS who responded were: strength training (38 PCPs [57%], 95 PTs [54%], and 32 OS [31%); weight management (36 PCPs [54%], 46 PTs [26%], and 59 OS [58%]); and activity modification (27 PCPs [41%], 28 PTs [22%], 41 OS [40%]). Additionally, 35 PTs (20%) reported that they provided motor control and biomechanical advice. However, few identified specific resources that they provided to their patients; 15 PCPs (17%), 11 PTs (5.1%), and 16 OS (12.2%), with the physicians (PCPs and OS) reporting the PT as the resource.

All HCP groups, in addition to identifying their own professional group as highly appropriate (82–99%), indicated that PTs were the appropriate professional to provide information about managing OA risk: 80% (95% CI 70–86) of PCPs, 99% (95% CI 96–100) of PTs, and 80% (95% CI 72–86) of OS (Table 5). OS were identified as the second most appropriate provider, followed by PCPs. Athletic therapists also were identified by 32–54% of respondents. Rheumatologists, kinesiologists, exercise physiologists, and PCPs were identified much less frequently.

DISCUSSION

It is well known that knee injury, commonly to the ACL, predisposes individuals to symptomatic knee OA (5–9). While research suggests that people with ACL injury have little knowledge of OA risk post-injury and its management (7,16,17), our work suggests that this knowledge gap, at least in part, may be a result of inconsistent care practices of the HCPs commonly managing people with ACL injury. Our findings indicate that HCPs, particularly PTs, who routinely treat people with ACL injury do not consistently discuss OA risk post-injury. According to our respondents, discussions generally occur at the time of initial injury management by OS and PCPs and to a lesser extent through 3 to 6 months post-injury, when the focus is likely on recovery from the acute injury by OS, PCPs, and PTs. There is limited discussion of potentially modifiable OA risk factors or their management, with most of the focus on reinjury. Finally, there is a disconnect because despite all HCP groups identifying PTs in addition to themselves as a resource for discussing OA risk and risk management, only 34% of PTs reported always doing so. These findings suggest that any intervention attempting to limit the development or progression of symptomatic OA in people with ACL injury needs to target both patients and HCPs.

Our work identified the fact that 71% of PCPs and 77% of OS always discussed OA risk with their patients and that the discussion most frequently occurred as part of initial injury management compared to only 34% of PTs. Given that PTs have more frequent and extended interaction with people who are undergoing

Table 4. Timing in relation to injury of osteoarthritis risk discussion*

	Primary care physician (n = 98)	Physical therapist (n = 263)	Orthopedic surgeon (n = 140)
As part of initial ACL management	74 (78.7); 70.3, 87.0	129 (54.0); 47.7, 60.3	128 (93.4); 89.3, 97.6
3–6 months post-injury	40 (42.6); 33.4–53.2	106 (44.3); 38.1, 50.6	18 (13.1); 7.5, 18.8
>6–12 months post-injury	23 (24.5); 17.1–34.4	63 (26.4); 20.8, 31.9	21 (15.3); 9.3, 22.4
>12 months post-injury	18 (19.1); 12.6–28.5	41 (17.1); 12.4, 21.9	16 (11.7); 6.3, 17.1
Do not discuss	2 (2.1); 0.6–0.8	5 (2.1); 0.3, 3.9	3 (2.2); 0.8–6.3
Missing, no.	4	24	3

* Values are the number (%); 95% confidence interval. ACL = anterior cruciate ligament.

rehabilitation after ACL injury, they have the opportunity to discuss and provide strategies for addressing OA risk. OS and PCPs have less frequent follow-up interactions in the year following ACL injury, but there is opportunity to discuss and reinforce OA risk and mitigation strategies at these times.

The low proportion of PTs discussing OA risk was somewhat surprising. Some literature has considered PT knowledge of and use of evidence in their practice. A systematic review by da Silva et al found that therapists considered evidence-based practice important but reported barriers to the use of scientific literature (26). These barriers included lack of time and resources, generalization of results, and inability to interpret statistics. MacKay et al found that PTs treating people with early OA, while acknowledging evidence, relied on professional development activities and their professional experience in developing individual care plans (27). However, experience and professional development may not align with evidence. Hence, while PTs likely are aware of evidence, there are barriers to implementation. Strategies and supports for implementation may be important to increase PT discussions of OA risk.

We are unaware of knowledge products (28), e.g., from systematic reviews, guidelines, and quality indicators on ACL management, used in clinical practice that specifically address OA risk factors and how to manage them. With the exception of the FIFA ≥11 program for reinjury prevention, implemented in soccer programs, we were unable to identify programs that incorporate OA risk factor management post ACL injury (11).

Development of tools and structured professional development activities may be important for moving evidence into practice for PTs and other HCPs. Strategies to do so will need to include HCP and patient input. Recent work identified the importance of understanding and developing interventions that fit the context and setting of the provider's practice for successful implementation (29). Irrespective of the HCP providing patients with strategies to support OA risk management, all will need to deliver consistent messages about OA risk and risk management for successful implementation.

Despite several known modifiable risk factors for knee OA, our work found that reinjury was the most frequently discussed risk factor, with patients advised to avoid twisting and pivoting activities. Weight gain/obesity, muscle strength, and activity levels were less frequently discussed. Whittaker et al reviewed potentially modifiable risk factors and possible mitigating strategies for the development of posttraumatic OA in youth and young adults following ACL injury (25). There was a 4-fold increased risk of reinjury when individuals with ACL injury returned to sport before meeting return-to-sport criteria (30,31). Young adults were 2.5 times as likely to be overweight/obese after knee injury within 3–10 years (32,33). Twenty percent with an ACL tear never return to any activity (34), and there was a 1.6 increased odds of muscle weakness, particularly quadriceps weakness (35). Additionally, Whittaker et al reported that many of these factors themselves were associated with incomplete rehabilitation prior to return to sport, unbalanced or inadequate nutrition, and unrealistic expectations and beliefs about OA risk (25).

Advice on weight management, strengthening, and activity levels were most frequently discussed with ACL patients. However, ≤50% of HCP respondents reported providing such advice on a consistent basis. This gap is particularly concerning, given the known OA risk factors and the evidence, albeit theoretical and limited, identified for potentially modifying these risk factors in the review by Whittaker et al (25). Our results, with the evidence provided in Whittaker's narrative review, reinforce the need to educate HCPs to ensure that interventions to inform patients about OA risk and potential mitigating strategies are comprehensive in content.

This study has several limitations. We were unable to determine the true response rates to the surveys because we could not verify the true number of each HCP group who met the eligibility criteria. Also, we could not determine how many in each province or territory treat people with ACL injuries. Despite respondents from across the country, we cannot be sure our results are generalizable for Canada or other countries, or that the respondents are representative of those treating people with ACL injury. Finally, the PCPs in our sample were members of CASEM with special expertise in sports medicine and do not represent all PCPs.

In conclusion, our study identified a gap in education provided to patients about OA risk, risk factors, and possible mitigating strategies following ACL injury. Discussion of OA risk factors is inconsistent and currently provides limited information. There

Table 5. Health care provider recommended to provide information about osteoarthritis risk and management*

	Primary care physician (n = 98)	Physical therapist (n = 263)	Orthopedic surgeon (n = 140)
Orthopedic surgeon	57 (61.3); 51.1–70.6	138 (59.5); 53.1–65.6	111 (82.8); 75.6–88.3
Primary care sports physician	79 (84.9); 76.3, 90.8	77 (33.2); 27.5–39.5	73 (54.5); 46.0–62.7
Rheumatologist	15 (16.1); 10.0–24.9	24 (10.3); 7.1–14.9	7 (5.2); 2.6–13.4
Physical therapist	74 (79.6); 70.3–86.5	229 (98.7); 96.3–99.6	107 (79.9); 72.3–85.8
Kinesiologist	33 (35.5); 26.5–45.6	63 (27.2); 21.8–33.2	48 (35.8); 28.2–44.2
Exercise physiologist	24 (25.8); 16.9, 34.7	40 (17.2); 12.4, 22.1	33 (24.6); 18.1–32.6
Athletic therapist	50 (53.8); 54.4–73.5	74 (31.9); 26.2–42.4	68 (50.7); 42.3, 59.2
No response, no.	5	31	6

* Values are the number (%); 95% confidence interval. Respondents could choose multiple professionals.

is an urgent need and opportunity to limit the development and progression of symptomatic knee OA following ACL injury. Research suggests that individuals who are aware of their health risks are more likely to adopt strategies to limit their risk (17,36). Strategies will need to foster HCP training as well as intervention development, evaluation, and monitoring of uptake by HCPs and patients to robustly address this gap and enable implementation as a core component of care following ACL injury.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Davis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Davis, Chahal, Dwyer, Li, Marks, Cruz, Urquhart, Wilson, Cudmore, Nimmon, Ogilvie-Harris.

Acquisition of data. Davis, Wong, Steinhart, Urquhart.

Analysis and interpretation of data. Davis, Chahal, Wong, Steinhart, Dwyer, Li, Marks, Cruz, Urquhart, Wilson, Cudmore, Nimmon, Ogilvie-Harris.

REFERENCES

1. Snoeker BA, Roemer FW, Turkiewicz A, Lohmander S, Frobell RB, Englund M. Does early anterior cruciate ligament reconstruction prevent development of meniscal damage? Results from a secondary analysis of a randomised controlled trial. Br Sports Med 2020;54:612–7.
2. Belk JW, Kraeutler MJ, Carver TJ, McCarty EC. Knee osteoarthritis after anterior cruciate ligament reconstruction with bone-patellar tendon-bone versus hamstring tendon autograft: a systematic review of randomized controlled trials. Arthroscopy 2018;34:1358–65.
3. Papathanasiou I, Michalitsis S, Hantes ME, Vlychou M, Anastasopoulou L, Malizos KN, et al. Molecular changes indicative of cartilage degeneration and osteoarthritis development in patients with anterior cruciate ligament injury. BMC Musculoskelet Disord 2016;17:21.
4. Cinque ME, Dornan GJ, Chahla J, Moatshe G, LaPrade RF. High rates of osteoarthritis develop after anterior cruciate ligament surgery: an analysis of 4108 patients. Am J Sports Med 2018;46:2011–9.
5. Neuman P, Englund M, Kostogiannis I, Friden T, Roos H, Dahlberg LE. Prevalence of tibiofemoral osteoarthritis 15 years after nonoperative treatment of anterior cruciate ligament injury: a prospective cohort study. Am J Sports Med 2008;36:1717–25.
6. Kessler MA, Behrend H, Henz S, Stutz G, Rukavina A, Kuster MS. Function, osteoarthritis and activity after ACL-rupture: 11 years follow-up results of conservative versus reconstructive treatment. Knee Surg Sports Traumatol Arthrosc 2008;16:442–8.
7. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med 2007;35:1756–69.
8. Muthuri SG, McWilliams DF, Doherty M, Zhang W. History of knee injuries and knee osteoarthritis: a meta-analysis of observational studies. Osteoarthritis Cartilage 2011;19:1286–93.
9. Duncan KJ, Chopp-Hurley JN, Maly MR. A systematic review to evaluate exercise for anterior cruciate ligament injuries: does this approach reduce the incidence of knee osteoarthritis? Open Access Rheumatol 2016;8:1–16.
10. Wasserstein D, Huston LJ, Nwosu S, Kaeding CC, Parker RD, Wright RW, et al. KOOS pain as a marker for significant knee pain two and six years after primary ACL reconstruction: a Multicenter Orthopaedic Outcomes Network (MOON) prospective longitudinal cohort study. Osteoarthritis Cartilage 2015;23:1674–84.
11. Gagnier JJ, Morgenstern H, Chess L. Interventions designed to prevent anterior cruciate ligament injuries in adolescents and adults: a systematic review and meta-analysis. Am J Sports Med 2013;41:1952–62.
12. Meuffels DE, Poldervaart MT, Diercks RL, Fievez AW, Patt TW, Hart CP, et al. Guideline on anterior cruciate ligament injury. Acta Orthopaedica 2012;83:379–86.
13. Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS. A randomized trial of treatment for acute anterior cruciate ligament tears. N Engl J Med 2010;363:331–42.
14. Kaeding CC, Leger-St-Jean B, Magnussen RA. Epidemiology and diagnosis of anterior cruciate ligament injuries. Clin Sports Med 2017;36:1–8.
15. Mall NA, Chalmers PN, Moric M, Tanaka MJ, Cole BJ, Bach BR Jr, et al. Incidence and trends of anterior cruciate ligament reconstruction in the United States. Am J Sports Med 2014;42:2363–70.
16. Feucht MJ, Cotic M, Saier T, Minzlaff P, Plath JE, Imhoff AB, et al. Patient expectations of primary and revision anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 2016;24:201–7.
17. Bennell KL, van Ginckel A, Kean CO, Nelligan RK, French SD, Stokes M, et al. Patient knowledge and beliefs about knee osteoarthritis after anterior cruciate ligament injury and reconstruction. Arthritis Care Res (Hoboken) 2016;68:1180–5.
18. Swann C, Moran A, Piggot D. Defining elite athletes: issues in the study of expert performance in sport psychology. Psychol Sport Exerc 2015;16:3–14.
19. Bennell K, Hunter DJ, Vicenzo B. Long-term effects of sport: preventing and managing OA in the athlete. Nat Rev Rheumatol 2012;8:747–52.
20. Thomas AC, Hubbard-Turner T, Wikstrom EA, Palmieri-Smith RM. Epidemiology of posttraumatic osteoarthritis. J Athl Train 2017;52:491–6.
21. O'Neill TW, McCabe PS, McBeth J. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. Best Pract Res Clin Rheumatol 2018;32:312–26.
22. Vina ER, Kwoh CK. Epidemiology of osteoarthritis: literature update. Curr Opin Rheumatol 2018;30:160–7.
23. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019;27:1578–89.
24. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheumatol 2020;72:220–33.
25. Whittaker JL, Roos EM. A pragmatic approach to prevent posttraumatic osteoarthritis after sport or exercise-related joint injury. Best Pract Res Clin Rheumatol 2019;33:158–71.
26. Da Silva TM, da Cunha Menezes Costa L, Garcia AN, Costa LO. What do physical therapists think about evidence-based practice? A systematic review. Man Ther 2015;20:388–401.
27. MacKay C, Hawker GA, Jaglal SB. How do physical therapists approach management of people with early knee osteoarthritis? A qualitative study. Phys Ther 2020;100:295–306.
28. Graham ID, Logan J, Harrison M, Straus S, Tetroe J, Caswell W, et al. Lost in knowledge translation: time for a map? J Contin Educ Health Prof 2006;26:13–24.
29. French SD, Green SE, O'Connor DA, McKenzie JE, Francis JJ, Michie S, et al. Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the theoretical domains framework. Implement Sci 2012;7:38.
30. Kyritsis P, Bahr R, Landreau P, Miladi R, Witvrouw E. Likelihood of ACL graft rupture: not meeting six clinical discharge criteria before return to sport is associated with a four times greater risk of rupture. Br J Sports Med 2016;50:946e51.

31. Grindem H, Snyder-Mackler L, Moksnes H, Engebretsen L, Risberg MA. Simple decision rules can reduce reinjury risk by 84% after ACL reconstruction: the Delaware-Oslo ACL cohort study. Br J Sports Med 2016;50:804e8.
32. Toomey CM, Whittaker JL, Nettel-Aguirre A, Reimer RA, Woodhouse LJ, Ghali B, et al. Higher fat mass is associated with a history of knee injury in youth sport. J Orthop Sports Phys Ther 2017;47:80e7.
33. Myer GD, Faigenbaum AD, Foss KB, Xu Y, Khoury J, Dolan LM, et al. Injury initiates unfavourable weight gain and obesity markers in youth. Br J Sports Med 2014;48:1477e81.
34. Ardern CL, Taylor NF, Feller JA, Webster KE. Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. Br J Sports Med 2014;48:1543e52.
35. Oiestad BE, Juhl CB, Eitzen I, Thorlund JB. Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2015;23:171e7.
36. Janz NK, Becker MH. The health belief model: a decade later. Health Educ Q 1984;11:1–47.

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How Foot Progression Angle Affects Knee Adduction Moment and Angular Impulse in Patients With and Without Medial Knee Osteoarthritis: A Meta-Analysis

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Objective. To investigate effects of foot progression angle (FPA) modification on the first and second peaks of external knee adduction moment (EKAM) and knee adduction angular impulse (KAAI) in individuals with and without medial knee osteoarthritis (OA) during level walking.

Methods. PubMed, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and SPORTDiscus were searched from inception to February 2020 by 2 independent reviewers. Included studies compared FPA modification (toe-in or toe-out gait) interventions to lower EKAM and/or KAAI with natural walking. Studies were required to report the first or second peaks of EKAM or KAAI.

Results. Sixteen studies were included, and >85% of included patients were graded with Kellgren/Lawrence grade II–IV knee OA. Toe-in gait reduced the first EKAM peak (standardized mean difference [SMD] –0.75 [95% confidence interval (95% CI) –1.05, –0.45]) and KAAI (SMD –0.46 [95% CI –0.86, –0.07]), while toe-out gait reduced the second EKAM peak (SMD –1.04 [95% CI –1.34, –0.75]) in healthy individuals. For patients with knee OA, toe-out gait reduced the second EKAM peak (SMD –0.53 [95% CI –0.75, –0.31]) and KAAI (SMD –0.26 [95% CI –0.49, –0.03]), while toe-in gait did not affect both EKAM peaks and KAAI.

Conclusion. Discrepancy in biomechanical effects of FPA modification was demonstrated between individuals with and without medial knee OA. Compared with natural walking, both toe-in and toe-out gait may be more effective in lowering EKAM and KAAI in healthy individuals. Toe-out gait may reduce EKAM and KAAI in patients with mild-to-severe knee OA. There is insufficient data from patients with early-stage knee OA, indicating that future research is required.

INTRODUCTION

Osteoarthritis (OA) is characterized by degeneration and damage of the cartilage (1) and associated with symptoms of pain and functional limitations (2). Compared with the lateral compartment, the medial compartment of the knee joint is more likely to be affected by OA due to greater joint reaction force during gait (3). It is difficult to measure knee joint load in vivo. External knee adduction moment (EKAM) is used as a surrogate of the medial knee joint load (4).

The EKAM has 2 peaks during level walking, and the magnitude of the first peak (during early stance) is usually larger than the second peak (during late stance) (5). Patients with medial knee OA exhibit greater EKAM than their healthy counterparts (6). Both EKAM peaks are higher in patients with severe medial knee OA than in those with mild knee OA (6). The first EKAM peak is positively correlated with the progression of knee OA (7).

Noninvasive interventions (e.g., unloading brace [8,9] and wedged footwear [10,11]) aim to reduce the EKAM peaks during walking but have short-term effects. Gait retraining is an effective nonsurgical treatment to reduce medial knee joint load, and its effect is sustained for at least 6 months (12,13). Modifying foot progression angle (FPA) (i.e., toe-in or toe-out) is an approach to lower the EKAM peaks during walking (14–29). The FPA is defined as the angle between the long axis of the foot segment (i.e., the line between the heel and the second metatarsal head) and the

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SIGNIFICANCE & INNOVATIONS

- This is the first review to comprehensively synthesize studies investigating the effect of foot progression angle modification on medial knee loading in individuals with and without medial knee osteoarthritis.
- Compared with natural walking, both toe-in and toe-out gait may be more effective in lowering the external knee adduction moment and knee adduction angular impulse in healthy individuals.
- Only toe-out gait reduced the second peak of the external knee adduction moment and knee adduction angular impulse in patients with medial knee osteoarthritis.
- Only few studies examined patients with early-stage knee osteoarthritis, and future research should address this gap.

walking direction. Healthy individuals tend to have a larger range of FPA (14,22) than patients with knee OA (16,25) during natural walking.

The effects of toe-in and toe-out gait on EKAM in patients with knee OA are inconsistent. Toe-in gait may improve knee pain by reducing the first EKAM peak (30), while toe-out gait may alleviate symptoms by reducing the second EKAM peak (19,20). However, toe-in gait was found to increase the second EKAM peak, while toe-out gait resulted in an increase of the first EKAM peak in patients with knee OA (27).

Knee adduction angular impulse (KAAI) is defined as area under the EKAM curve over the stance phase (31) and is another key parameter for evaluating effectiveness of gait retraining (20,27). KAAI has been associated with loss of cartilage in the medial knee compartment (32) and accumulated medial knee joint load throughout the entire stance phase (31). One study reported that toe-in gait did not influence KAAI in patients with knee OA (24), while another reported that KAAI increased with toe-in gait and reduced with toe-out gait (27). The effect of toe-in gait on KAAI is inconsistent between healthy individuals (14,29) and patients with medial knee OA (24,27).

Previous reviews have summarized the effects of gait modification on the medial knee joint load (33,34). However, they did not compare the differences between healthy individuals and patients with medial knee OA or examine the effects of real-time biofeedback gait retraining. In addition, the effects on KAAI were not examined. Both reviews did not employ meta-analyses, and neither calculated the pooled effects from the included studies. The overall effect of FPA modification on EKAM and KAAI between individuals with and without knee OA remains unclear. It is important to examine the effects of other moderators (e.g., knee alignment and body mass index [BMI]), which may affect EKAM and KAAI (8,35,36).

The purposes of this review were as follows: 1) to summarize data from existing literature on the effect of walking with FPA modification on EKAM and KAAI in individuals with and without medial knee OA; and 2) to compare the effect of walking with FPA modification on EKAM and KAAI outcomes between individuals with and without medial knee OA. We conducted subgroup analyses to assess the effects of FPA modification on biomechanical variables by comparing individuals with different knee alignment and different BMI.

MATERIALS AND METHODS

The study protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (37). The protocol was registered on the PROSPERO International prospective registry of systematic reviews (ID CRD42019130534).

Search strategy. A comprehensive literature search was conducted in February 2020 using PubMed, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and SPORTDiscus without date restrictions. The search strategy included a combination of keywords involving synonyms of FPA, knee, load, and walk (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24420/abstract). All identified articles were imported to EndNote X9 (Thomson Reuters), which automatically removed duplicates. The remaining articles were initially screened by reviewing titles and abstracts. Those articles were further screened by reviewing full text to identify articles that fulfilled the predetermined selection criteria. All these procedures were independently conducted by 2 reviewers (SW and SM). Two reviewers discussed any discrepancies, and, if required, a third reviewer (RTHC) was consulted for reaching consensus.

Inclusion/exclusion criteria. The following inclusion criteria were adopted: 1) published in a peer-reviewed journal as a full article written in English; 2) included either healthy adults or patients with medial knee OA age 18 years or older; 3) included natural walking as a control condition and at least 1 experimental FPA modification condition (i.e., either toe-in or toe-out gait); and 4) included 1 of the main outcomes, i.e., the first and/or second EKAM peaks and/or KAAI.

The following exclusion criteria were adopted: 1) case reports, conference abstracts, and systematic reviews; 2) studies investigating participants who underwent any knee surgeries; 3) studies with interventions that combined gait modifications (e.g., trunk side bending or knee thrust gait); and 4) studies assessing participants during activities other than level ground walking (e.g., stair climbing).

Data extraction. Two reviewers (SW and SM) independently extracted data regarding study design, sample size, participant characteristics, gait modification (toe-in/toe-out), training method, and mean and SD of the first and second EKAM peaks and KAAI. If studies did not report results numerically,

the corresponding authors of those studies were contacted by email for extra information. Studies with missing information were excluded if the authors did not respond to our requests for clarification.

Risk of bias within included studies. Two reviewers independently assessed the risk of bias of each included studies using the modified Downs and Black quality checklist (38), which consists of 26 of 27 items of the original checklist (39). The item related to statistical power was removed due to its ambiguity (40). The rating of each item ranges from 0 (poor) to 1 (good), except item 5 has 3 levels of score (0 [poor], 1 [fair], and 2 [good]). The total score ranges from 0 to 27, and a checklist score of 14 was set as the inclusion threshold for data synthesis (38). Two reviewers attempted to resolve disagreements through a face-to-face discussion. If consensus was not achieved, a third reviewer (RTHC) was consulted.

Data synthesis and analysis. Meta-analysis was performed using Review Manager (RevMan 5.3). We calculated standardized mean difference (SMD) with 95% confidence intervals (95% CIs) from the meta-analysis to estimate the overall effect sizes, which were interpreted using Cohen's *d* criteria (minimal [<0.2], small [0.2–0.49], medium [0.50–0.79], and large [≥0.8]) (41). We also compared the effect between groups using the chi-square test. The I^2 index was used to measure heterogeneity across included studies. We considered an I^2 index of 50% or less to indicate low heterogeneity, and a fixed-effects model was used for analyses; otherwise, a random-effects model was performed (42).

Publication bias was assessed graphically using funnel plots and quantitatively by Egger's regression test using Comprehensive Meta-Analysis, version 3 (Biostat). *P* values less than 0.1 (2-tailed) were considered as indicating the presence of publication bias (43).

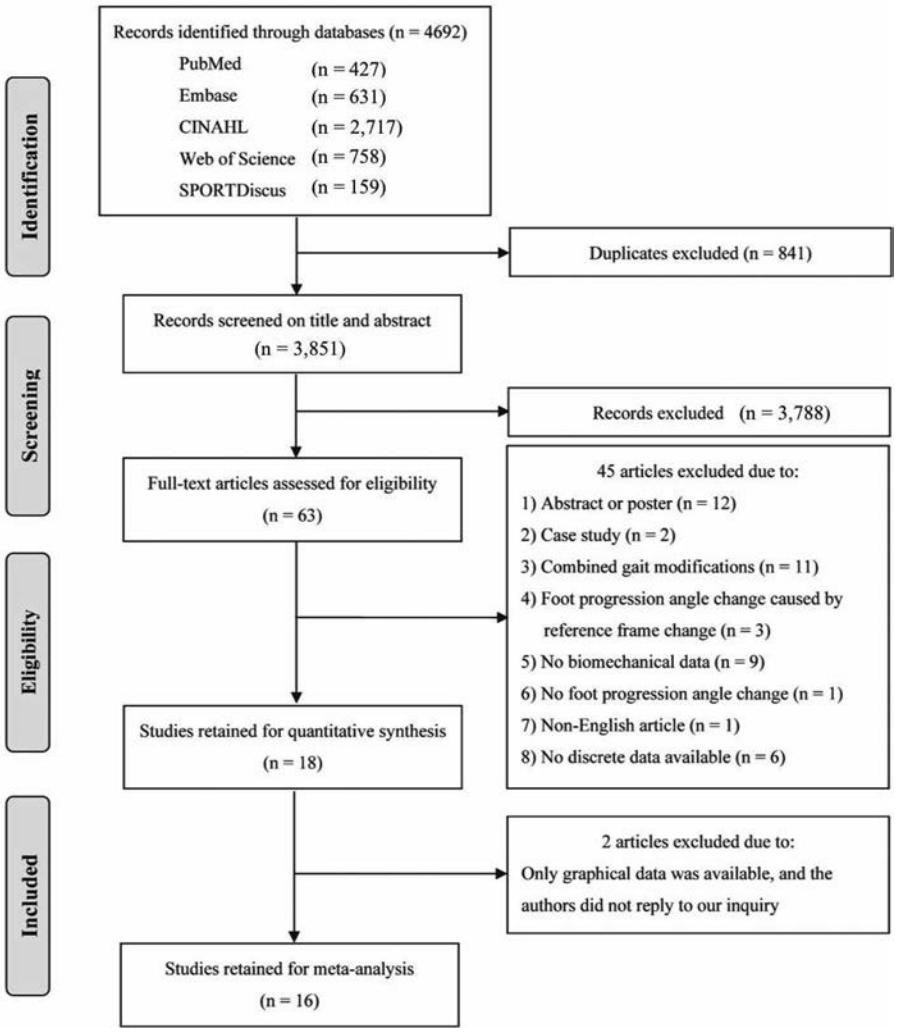

Figure 1. Procedure and flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method for study screening and inclusion. CINAHL = Cumulative Index to Nursing and Allied Health Literature.

Table 1. Characteristics of the 16 studies included*

Author, year (ref.)	No. of patients (M/F)	Age, mean ± SD years	BMI, mean ± SD kg/m^2	Knee alignment angle, mean ± SD degrees†	Sample	Walking speed, mean ± SD meters/sec	Gait modification	Description of the training	QI
Bennett et al, 2017 (14)	38 (NR)	Neutral group: 23.7 ± 0.8; valgus group: 22.3 ± 1.0; varus group: 24.7 ± 0.9	Neutral group: 23.6 ± 3.1; valgus group: 23.7 ± 2.5; varus group: 23.3 ± 4.1	Neutral group: 0.6 ± 0.7; valgus group: 3.6 ± 1.0; varus group: 6.0 ± 1.4	Healthy adults with neutral (n = 15), valgus (n = 13), and varus (n = 10) knee alignment	Controlled within ±5% of their average speed	Toe-in	Visual guidance by 3 sets of adhesive tape strips (placed at 10°), and visual feedback was provided via a mirror at the end of the walkway	22
Caldwell et al, 2013 (15)	12 (6/6)	21.0 ± 1.7	22.4 ± 1.5	NR	Healthy adults	Controlled speed within ±5% of 1.47 meters/sec	Toe-out	Verbal instruction and demonstration; feedback from the investigator	21
Charlton et al, 2019 (16)	15 (6/9)	67.9 ± 9.4	NR (height = 1.67 ± 0.11 meters; weight = 75.6 ± 15.0 kg)	NR	Adults with medial knee OA (K/L grade II [n = 7], K/L grade III [n = 8])	Controlled within ±5% of natural walking speed	Toe-in and toe-out	Real-time biofeedback	21
Gerbrands et al, 2014 (17)	37 (10/27)	43.4 ± 12.2	NR (height = 175.4 ± 7.8 cm; weight = 72.1 ± 11.7 kg)	3.2 ± 3.7	Healthy adults	Self-selected comfortable speed	Toe-out	Verbal feedback from the investigator	22
Guo et al, 2007 (18)	10 (6/4)	64.0 ± 8.0	29.0 ± 5.6	NR	Adults with mild-to-moderate medial knee OA (K/L grade I–III)	Monitored consistency within subject	Toe-out	Ink lines were drawn on the force plate to guide foot placement for the increased FPA	18
Hunt et al, 2018 (19)	79 (24/55)	Control group: 65.4 ± 9.6; toe-out group: 64.6 ± 7.6	Control group: 27.4 ± 3.5; toe-out group: 27.3 ± 3.5	NR	Adults with mild-to-severe medial knee OA (control group: K/L grade II [n = 18], K/L III [n = 14], K/L IV [n = 7]; knee OA group: K/L grade II [n = 19], K/L III [n = 17], K/L IV [n = 4])	Self-selected speed	Toe-out	Green tape on the mirror to best cover the reflection of the foot in this target position during the training session to guide foot placement during treadmill training walking	24

(Continued)

Table 1. *(Cont'd)*

Author, year (ref.)	No. of patients (M/F)	Age, mean ± SD years	BMI, mean ± SD kg/m^2	Knee alignment angle, mean ± SD degrees†	Sample	Walking speed, mean ± SD meters/sec	Gait modification	Description of the training	QI
Hunt and Takacs, 2014 (20)	16 (7/9)	64.8 ± 10.4	29.9 ± 6.8	NR	Adults with medial knee OA (K/L grade II [n = 4], K/L III [n = 9], K/L IV [n = 3])	Controlled within ±5% of baseline	Toe-out	Real-time biofeedback of performance	21
Lynn and Costigan, 2008 (21)	24 (12/12)	Healthy group: 68.7 ± 8.4; OA group: 67.4 ± 10.0	Healthy group: 23.2 ± 2.8; OA group: 27.3 ± 3.8	Healthy group: 3.1 ± 2.6; OA group: 0.6 ± 4.9	12 healthy adults and 12 adults with knee OA (K/L grade II III)	Walking speed was not controlled	Toe-in and toe-out	Toe-out: walk with foot externally rotated as much as possible; toe in: walk with foot internally rotated as much as possible	18
Lynn et al, 2008 (22)	11 (6/5)	22.9 ± 1.8	NR (height = 167.7 ± 11.5 cm; weight = 72.4 ± 14.4 kg)	NR	Healthy university students	Constant speed	Toe-in and toe-out	Parallel lines of tape were placed onto the floor such that when walking, the subject's foot would have to fill the gap between the tape lines	21
Ogaya et al, 2015 (23)	18 (8/10)	20.7 ± 0.8	NR (height = 164.4 ± 8.9 cm; weight = 59.9 ± 8.2 kg)	NR	Healthy adults	Self-selected walking speed	Toe-out	Instructed to walk normally on the force plate (normal gait), or to walk with their feet angled outward, angling the foot outwards relative to the long axis of the leg (toe-out gait)	18
Richards et al, 2018 (24)	35 (13/22)	62.3 ± 5.9	25.5 ± 2.6	NR	Adults with medial knee OA (K/L grade I [n = 16], K/L II [n = 7], K/L III [n = 8], K/L IV [n = 4])	Fixed speed after self-selected comfortable walking	Toe-in	Real-time feedback based on a predefined target for the modification	18
Shull et al, 2015 (25)	10 (6/4)	60.0 ± 13.0	26.6 ± 4.7	NR	Adults with symptomatic medial knee OA (K/L grade II [n = 3], K/L III [n = 6], K/L IV [n = 1])	Split-belt treadmill at a preferred speed 1.22 ± 0.21	Toe-in	Real-time feedback	19

(Continued)

Table 1. *(Cont'd)*

Author, year (ref.)	No. of patients (M/F)	Age, mean ± SD years	BMI, mean ± SD kg/m^2	Knee alignment angle, mean ± SD degrees†	Sample	Walking speed, mean ± SD meters/sec	Gait modification	Description of the training	QI
Shull et al, 2013 (26)	12 (7/5)	59.8 ± 12.0	26.5 ± 4.2	NR	Adults with symptomatic medial knee OA (K/L grade II [n = 4], K/L III [n = 7], K/L IV [n = 1])	Split-belt treadmill at a preferred speed 1.23 ± 0.21	Toe-in	Real-time haptic (touch) feedback	22
Simic et al, 2013 (27)	22 (9/13)	69.7 ± 9.0	28.4 ± 4.8	2.6 ± 4.7	Adults with medial knee OA (K/L grade II [n = 11], K/L III [n = 6], K/L IV [n = 5])	Controlled within ±5% of natural speed	Toe-in and toe-out	Real-time movement biofeedback	23
Uhlrich et al, 2018 (28)	20 (NR)	26 ± 5	NR	NR	Healthy adults	Comfortable walking speed 1.15 ± 0.10	Toe-in and toe-out	Vibrotactile feedback: an unsuccessful step when the FPA was not within 2° of each trial's target angle	18
Van den Noort et al, 2013 (29)	14 (6/8)	23.8 ± 3.9	NR (height = 1.81 ± 0.11 meters; weight = 72.7 ± 16.3 kg)	NR	Healthy young adults	Fixed self-selected normal walking speed	Toe-in and toe-out	Tape was stuck to the floor on either side of the walkway, and the trials were video taped	23

* BMI = body mass index; F = female; FPA = foot progression angle; K/L = Kellgren/Lawrence; M = male; NR = not reported; OA = osteoarthritis; QI = quality index of the modified Downs and Black checklist; ref. = reference.
† According to Bennett et al (14), normal knee alignment: –2° < knee alignment angle <2°; knee valgus: knee alignment angle >2°; knee varus: knee alignment angle less than –2°.

RESULTS

A total of 4,692 records were identified in the initial search. After screening, 18 studies met the inclusion criteria (Figure 1). Two studies were excluded from the 18 studies, as the authors did not respond to our requests for additional information. Among the remaining 16 studies, one study (24) reported the first EKAM peak using median and interquartile range instead of mean and SD. That study met our inclusion criteria but was not included in the meta-analysis. Data from the remaining 16 studies were used for data synthesis (Figure 1).

Characteristics of included studies. The 16 studies yielded a total of 373 individuals. The subject characteristics are presented in Table 1. Of the 16 studies, 15 studies adopted a repeated-measures design, and one study (19) was a randomized controlled trial. Four studies compared toe-in gait with natural gait, 6 studies compared toe-out gait with natural gait, and the remaining 6 studies compared both toe-in and toe-out gait with natural gait. Seven studies recruited only healthy individuals, 8 studies involved only patients with medial knee OA, and one (21) included both healthy individuals and patients with knee OA. For those studies involving patients with knee OA, 185 of 211 patients were diagnosed with Kellgren/Lawrence (K/L) grade II–IV knee OA. Eleven of 16 studies defined toe-out gait as positive FPA, and we adopted this definition in the present review. Four studies (14,17,21,27) included knee alignment measurement. Three of them used long-leg radiographs (14,21,27), and another study measured knee alignment with surface markers (17). Bennett et al classified participants by knee alignment using the following categories: neutral ($-2^o \leq$ alignment angle $\leq 2^o$), valgus (alignment angle $>2^o$), and varus (alignment angle less than -2^o) (14). Ten studies (14,15,18–21,24–27) reported BMI; 5 studies (16,17,22,23,29) reported body weight and height, and one study (28) reported neither BMI, body weight, nor height.

Risk of bias. The risk of bias of included studies was evaluated using the modified Downs and Black quality checklist, with scores ranging from 18 to 24 (Table 1). A median score of 21 of 27 indicates a moderate methodological quality (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24420/abstract). The overall agreement between the 2 independent reviewers was high (Cohen's $\kappa = 0.93$). Regarding individual items, agreement was mostly achieved except for item number 5 (3 of 16, 19%), item number 8 (2 of 16, 13%), item number 15 (3 of 16, 19%), and item number 16 (1 of 16, 6%). Most studies had low risk for reporting bias (item numbers 1–10) and some risk for selection, performance, and detection bias. Patient and personnel blinding (item numbers 14 and 15) were not possible in all studies.

Funnel plots are shown in Supplementary Figures 1 and 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24420/abstract. Egger's regression intercepts for toe-in and toe-out gait were respectively –3.44 ($P = 0.02$) and 0.91 ($P = 0.40$) on the first EKAM peak, 1.50 ($P = 0.27$) and –1.34 ($P = 0.41$) on the second EKAM peak, and –3.01 ($P = 0.11$) and 1.31 ($P = 0.33$) on KAAI. Publication bias was only present in the studies investigating toe-in gait on the first EKAM peak. Subgroup analysis revealed that the Egger's regression intercepts were –1.76 ($P = 0.18$) and 1.50 ($P = 0.27$) for the healthy and knee OA groups, respectively, indicating that publication bias was not presented in both subgroups.

Medial knee joint load. *First EKAM peak.* Four studies (14,16,19,27) employed multiple FPA modifications (Table 2), resulting in 14 comparisons between toe-in and natural gait (Figure 2A) and 17 comparisons between toe-out gait and natural gait (Figure 2B) considering the first EKAM peak as outcome measure.

The overall pooled effect indicated that toe-in gait significantly reduced the first EKAM peak (Figure 2A). Subgroup comparisons revealed that the first EKAM peak significantly reduced in the healthy group ($P < 0.001$) but remained unchanged in the knee OA group ($P = 0.06$). When performing between-group comparisons, the effect of toe-in gait on the first EKAM peak significantly reduced in healthy individuals when compared to patients with knee OA ($\chi^2 = 5.79$, $P = 0.02$). We found similar effects of toe-in gait on the first EKAM peak regardless of BMI and knee alignments (see Supplementary Table 2 and Supplementary Figure 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24420/abstract). However, toe-in gait did not appear to change the first EKAM peak in elderly healthy individuals ($P = 0.31$) (see Supplementary Table 2 and Supplementary Figure 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24420/abstract).

Toe-out gait did not reduce the first EKAM peak (Figure 2B). Subgroup analyses yielded similar pooled effect in both healthy ($P = 0.42$) and knee OA groups ($P = 0.43$). We also found similar effect of toe-out gait on the first EKAM peak in individuals across age, BMI, and knee alignment (see Supplementary Table 2 and Supplementary Figure 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24420/abstract).

Second EKAM peak. Some studies included multiple comparisons between toe-in (14,16,27) or toe-out gait (16,19,27) versus natural gait. Hence, there were 14 and 17 comparisons between toe-in (Figure 3A) or toe-out (Figure 3B) gait versus natural gait considering the second EKAM peak as outcome measure.

The overall pooled effect suggested that toe-in gait significantly increased the second EKAM peak (Figure 3A). However, subgroup comparisons demonstrated insignificant changes of the second EKAM peak in both healthy individuals ($P = 0.13$) and patients with knee OA ($P = 0.08$). This trend was consistent in

Table 2. Main results of the 16 studies included*

Study	Target gait modification	FPA (degrees)		Unit		
		Modified gait, mean ± SD	Natural gait, mean ± SD		Modified gait, mean ± SD	Natural gait mean ± SD
First peak of KAM						
Bennett et al, 2017 (14)	Increased toe-in targeted at 10° (neutral group)	–15.7 ± 4.8†	2.8 ± 5.6†	Nm/kg	0.32 ± 0.10	0.48 ± 0.12
	Increased toe-in targeted at 10° (valgus group)	–17.4 ± 4.6†	–0.83 ± 5.9†	Nm/kg	0.22 ± 0.14	0.35 ± 0.12
	Increased toe-in targeted at 10° (varus group)	–13.7 ± 3.8†	5.8 ± 7.0†	Nm/kg	0.46 ± 0.10	0.64 ± 0.18
Caldwell et al, 2013 (15)	Toe-out	21.4 ± 5.0	10.2 ± 4.4	Nm/kg × meters	0.321 ± 0.099	0.322 ± 0.097
Charlton et al, 2019 (16)	Toe-in (10°)	–9.6 ± 1.4†	7.7 ± 8.1†	Nm/kg	0.40 ± 0.14‡	0.48 ± 0.14‡
	Toe-in (0 rotation)	0.2 ± 1.4†	7.7 ± 8.1†	Nm/kg	0.44 ± 0.13‡	0.48 ± 0.14‡
	Toe-out (–10°)	10.3 ± 1.4†	7.7 ± 8.1†	Nm/kg	0.48 ± 0.14‡	0.48 ± 0.14‡
	Toe-out (–20°)	19.8 ± 1.4†	7.7 ± 8.1†	Nm/kg	0.51 ± 0.14‡	0.48 ± 0.14‡
Gerbrands et al, 2014 (17)	Toe-out	13.6 ± 2.4	0.1 ± 3.1	Nm/(BW × Ht)	0.22 ± 0.06	0.21 ± 0.04
Guo et al, 2007 (18)	Increased toe-out 15°	18.6 ± 8.9	2.0 ± 6.8	%BW × Ht	2.84 ± 0.44	2.81 ± 0.49
Hunt et al, 2018 (19)	Toe-out (walking with additional 15°)	14.8 ± 4.5†	5.7 ± 4.5†	%BW × Ht	2.43 ± 0.36	2.57 ± 0.34
	Toe-out	12.6 ± 4.1	5.8 ± 4.1	%BW × Ht	2.41 ± 0.41	2.57 ± 0.40
Hunt and Takacs, 2014 (20)	Toe-out (increased by ≥10°)	11.4 ± 6.5	4.8 ± 6.6	%BW × Ht	3.19 ± 0.72	3.45 ± 0.82
Lynn and Costigan, 2008 (21)	Toe-in (healthy group)	2.5 ± 6.4†	11.5 ± 4.7†	Nm/kg	0.32 ± 0.12	0.37 ± 0.11
	Toe-out (healthy group)	22.5 ± 5.0†	11.5 ± 4.7†	Nm/kg	0.36 ± 0.13	0.37 ± 0.11
	Toe-in (OA group)	–4.4 ± 6.4†	7.5 ± 5.9†	Nm/kg	0.43 ± 0.15	0.45 ± 0.13
	Toe-out (OA group)	17.1 ± 8.0†	7.5 ± 5.9†	Nm/kg	0.46 ± 0.13	0.45 ± 0.13
Lynn et al, 2008 (22)	Toe-in	–9.1 ± 7.9	18.5 ± 8.2	Nm/kg	0.28 ± 0.16	0.31 ± 0.16
	Toe-out	40.2 ± 8.7	18.5 ± 8.2	Nm/kg	0.35 ± 0.18	0.31 ± 0.16
Ogaya et al, 2015 (23)	Toe-out	19.1 ± 8.0	5.1 ± 7.0	Nm/%BW × Ht	3.26 ± 1.20	3.62 ± 1.32
Shull et al, 2015 (25)	Increased toe-in	–5.1 ± 5.1	2.1 ± 4.0	%BW × Ht	2.61 ± 1.47	3.11 ± 1.40
Shull et al, 2013 (26)	Increased toe-in	–2.1 ± 6.3	3.3 ± 4.5	%BW × Ht	2.90 ± 1.38	3.28 ± 1.37
Simic et al, 2013 (27)	Toe-in	–9.7 ± 3.3	4.5 ± 3.3	Nm/(BW × Ht)%	3.48 ± 1.12	3.74 ± 1.12
	Toe-in	–2.3 ± 3.3	4.5 ± 3.3	Nm/(BW × Ht)%	3.65 ± 1.12	3.74 ± 1.12
	Toe-out	5.3 ± 3.3	4.5 ± 3.3	Nm/(BW × Ht)%	3.74 ± 1.12	3.74 ± 1.12
	Toe-out	12.6 ± 3.3	4.5 ± 3.3	Nm/(BW × Ht)%	3.92 ± 1.12	3.74 ± 1.12
	Toe-out	20.8 ± 3.3	4.5 ± 3.3	Nm/(BW × Ht)%	4.09 ± 1.12	3.74 ± 1.12
Uhlrich et al, 2018 (28)	10° toe-in	–7.3 ± 3.6	2.6 ± 3.7	%BW × Ht	2.59 ± 1.00	2.86 ± 0.92
	10° toe-out	12.4 ± 3.7	2.6 ± 3.7	%BW × Ht	2.74 ± 1.12	2.86 ± 0.92
Van den Noort et al, 2013 (29)	Toe-in	–10.0 ± 3.5	8.7 ± 1.7	%BW × Ht	2.03 ± 1.65	3.71 ± 0.86
	Toe-out	24.2 ± 1.5	8.3 ± 1.6	%BW × Ht	4.70 ± 1.12	3.78 ± 0.82
Second peak of KAM						
Bennett et al, 2017 (14)	Increased toe-in targeted at 10° (neutral group)	–15.7 ± 4.8†	2.8 ± 5.6†	Nm/kg	0.40 ± 0.10	0.37 ± 0.11
	Increased toe-in targeted at 10° (valgus group)	–17.4 ± 4.6†	–0.83 ± 5.9†	Nm/kg	0.30 ± 0.14	0.26 ± 0.10
	Increased toe-in targeted at 10° (varus group)	–13.7 ± 3.8†	5.8 ± 7.0†	Nm/kg	0.57 ± 0.17	0.50 ± 0.11
Caldwell et al, 2013 (15)	Toe-out	21.4 ± 5.0	10.2 ± 4.4	Nm/kg × meters	0.119 ± 0.057	0.176 ± 0.059
Charlton et al, 2019 (16)	Toe-in (10°)	–9.6 ± 1.4†	7.7 ± 8.1†	Nm/kg	0.47 ± 0.13‡	0.39 ± 0.14‡
	Toe-in (0 rotation)	0.2 ± 1.4†	7.7 ± 8.1†	Nm/kg	0.42 ± 0.12‡	0.39 ± 0.14‡
	Toe-out (–10°)	10.3 ± 1.4†	7.7 ± 8.1†	Nm/kg	0.37 ± 0.13‡	0.39 ± 0.14‡
	Toe-out (–20°)	19.8 ± 1.4†	7.7 ± 8.1†	Nm/kg	0.32 ± 0.13‡	0.39 ± 0.14‡
Gerbrands et al, 2014 (17)	Toe-out	13.6 ± 2.4	0.1 ± 3.1	Nm/(BW × Ht)	0.11 ± 0.04	0.18 ± 0.05
Guo et al, 2007 (18)	Increased toe-out 15°	18.6 ± 8.9	2.0 ± 6.8	%BW × Ht	1.37 ± 0.53	2.27 ± 0.63
Hunt et al, 2018 (19)	Toe-out (walking with additional 15°)	14.8 ± 4.5†	5.7 ± 4.5†	%BW × Ht	2.44 ± 0.30	2.69 ± 0.40
	Toe-out	12.6 ± 4.1†	5.8 ± 4.1†	%BW × Ht	2.50 ± 0.41	2.70 ± 0.40
Hunt and Takacs, 2014 (20)	Toe-out (increased by ≥10°)	11.4 ± 6.5	4.8 ± 6.6	%BW × Ht	2.57 ± 0.84	2.87 ± 0.92
Lynn and Costigan, 2008 (21)	Toe-in (healthy group)	2.5 ± 6.4†	11.5 ± 4.7†	Nm/kg	0.26 ± 0.09	0.27 ± 0.12
	Toe-out (healthy group)	22.5 ± 5.0†	11.5 ± 4.7†	Nm/kg	0.19 ± 0.14	0.27 ± 0.12
	Toe-in (OA group)	–4.4 ± 6.4†	7.5 ± 5.9†	Nm/kg	0.39 ± 0.14	0.40 ± 0.14
	Toe-out (OA group)	17.1 ± 8.0†	7.5 ± 5.9†	Nm/kg	0.31 ± 0.13	0.40 ± 0.14

(Continued)

Table 2. *(Cont'd)*

Study	Target gait modification	FPA (degrees)		Unit		
		Modified gait, mean ± SD	Natural gait, mean ± SD		Modified gait, mean ± SD	Natural gait mean ± SD
Lynn et al, 2008 (22)	Toe-in	−9.1 ± 7.9	18.5 ± 8.2	Nm/kg	0.41 ± 0.14	0.25 ± 0.16
	Toe-out	40.2 ± 8.7	18.5 ± 8.2	Nm/kg	0.02 ± 0.16	0.25 ± 0.16
Ogaya et al, 2015 (23)	Toe-out	19.1 ± 8.0	5.1 ± 7.0	Nm/%BW × Ht	2.61 ± 1.10	3.57 ± 1.17
Richards et al, 2018 (24)	Toe-in	NR	NR	%BW × Ht	2.47 ± 0.78	2.50 ± 0.79
Shull et al, 2015 (25)	Increased toe-in	−1.4 ± 6.4	3.9 ± 4.6	%BW × Ht	1.94 ± 1.09	1.98 ± 1.14
Simic et al, 2013 (27)	Toe-in	−9.7 ± 3.3†	4.5 ± 3.3†	Nm/(BW × Ht)%	2.58 ± 0.78	2.11 ± 0.77
	Toe-in	−2.3 ± 3.3†	4.5 ± 3.3†	Nm/(BW × Ht)%	2.37 ± 0.78	2.11 ± 0.77
	Toe-out	5.3 ± 3.3†	4.5 ± 3.3†	Nm/(BW × Ht)%	2.09 ± 0.77	2.11 ± 0.77
	Toe-out	12.6 ± 3.3†	4.5 ± 3.3†	Nm/(BW × Ht)%	1.78 ± 0.77	2.11 ± 0.77
	Toe-out	20.8 ± 3.3†	4.5 ± 3.3†	Nm/(BW × Ht)%	1.36 ± 0.77	2.11 ± 0.77
Uhlrich et al, 2018 (28)	10° toe-in	−7.3 ± 3.6	2.6 ± 3.7	%BW × Ht	2.00 ± 0.85	2.04 ± 0.88
	10° toe-out	12.4 ± 3.7	2.6 ± 3.7	%BW × Ht	1.51 ± 0.73	2.04 ± 0.88
Van den Noort et al, 2013 (29)	Toe-in	−10.0 ± 3.5	8.7 ± 1.7	%BW × Ht	2.03 ± 1.42	2.02 ± 1.05
	Toe-out	24.2 ± 1.5	8.3 ± 1.6	%BW × Ht	0.91 ± 0.86	2.05 ± 0.94
KAAI						
Bennett et al, 2017 (14)	Increased toe-in targeted at 10° (neutral group)	−15.7 ± 4.8†	2.8 ± 5.6†	Nms/kg	0.15 ± 0.05	0.16 ± 0.04
	Increased toe-in targeted at 10° (valgus group)	−17.4 ± 4.6†	−0.8 ± 5.9†	Nms/kg	0.12 ± 0.04	0.14 ± 0.04
	Increased toe-in targeted at 10° (varus group)	−13.7 ± 3.8†	5.8 ± 7.0†	Nms/kg	0.18 ± 0.05	0.2 ± 0.06
Caldwell et al, 2013 (15)	Toe-out	21.4 ± 5.0	10.2 ± 4.4	Nms/kg m	0.074 ± 0.026	0.086 ± 0.023
Gerbrands et al, 2014 (17)	Toe-out	13.6 ± 2.4	0.1 ± 3.1	Nms/(BW × Ht)	0.07 ± 0.03	0.08 ± 0.03
Hunt et al, 2018 (19)	Toe-out (walking with additional 15°)	14.8 ± 4.5†	5.7 ± 4.5†	%BW × Ht × sec	0.82 ± 0.12	0.87 ± 0.11
	Toe-out	12.6 ± 4.1†	5.8 ± 4.1†	%BW × Ht × sec	0.81 ± 0.12	0.87 ± 0.11
Hunt and Takacs, 2014 (20)	Toe-out (increased by ≥10°)	11.4 ± 6.5	4.8 ± 6.6	%BW × Ht × sec	1.24 ± 0.34	1.33 ± 0.29
Richards et al, 2018 (24)	Toe-in	NR	NR	%BW × Ht × sec	1.07 ± 0.40	1.10 ± 0.40
Simic et al, 2013 (27)	Toe-in	−9.7 ± 3.3†	4.5 ± 3.3†	Nms/(BW × Ht)%	1.3 ± 0.47	1.23 ± 0.47
	Toe-in	−2.3 ± 3.3†	4.5 ± 3.3†	Nms/(BW × Ht)%	1.29 ± 0.45	1.23 ± 0.47
	Toe-out	5.3 ± 3.3†	4.5 ± 3.3†	Nms/(BW × Ht)%	1.25 ± 0.45	1.23 ± 0.47
	Toe-out	12.6 ± 3.3†	4.5 ± 3.3†	Nms/(BW × Ht)%	1.21 ± 0.45	1.23 ± 0.47
	Toe-out	20.8 ± 3.3†	4.5 ± 3.3†	Nms/(BW × Ht)%	1.17 ± 0.47	1.23 ± 0.47
Van den Noort et al, 2013 (29)	Toe-in	−10.0 ± 3.5	8.7 ± 1.7	%BW × Ht × sec	0.8 ± 0.45	1.14 ± 0.34
	Toe-out	24.2 ± 1.5	8.3 ± 1.6	%BW × Ht × sec	1.11 ± 0.34	1.12 ± 0.34

* BW = body weight; FPA = foot progression angle; Ht = height; KAAI = knee adduction angular impulse; KAM = knee adduction moment; NR = not reported.
† The definition of toe-in gait and toe-out gait in the original studies was opposite to that in the majority of studies and then translated to the definition used in the majority of studies.
‡ Data obtained from personal communication with the authors.

individuals with different age, BMI, and knee alignment (see Supplementary Table 2 and Supplementary Figure 5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24420/abstract).

The overall pooled estimation demonstrated a significant reduction in the second EKAM peak during toe-out gait (Figure 3B). Subgroup comparisons yielded similar pooled results, except patients with normal knee alignment did not show a reduction of the second EKAM peak with toe-out gait ($P = 0.13$) (see Supplementary Table 2 and Supplementary Figure 6, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24420/abstract). Toe-out gait significantly reduced the second EKAM peak in both healthy ($P < 0.001$) and knee OA groups ($P < 0.001$). However, reduction of the second EKAM peak was significantly higher in the healthy group than in the knee OA group ($\chi^2 = 9.31$, $P = 0.002$).

KAAI. Similar to EKAM, some studies included multiple comparisons of toe-in (14,27) and toe-out gaits (19,27) with different FPAs. There were 7 and 9 comparisons of toe-in (Figure 4A) and toe-out gait (Figure 4B) effects on KAAI, respectively.

The overall pooled effect suggested insignificant change of KAAI during toe-in gait (Figure 4A). Subgroup comparisons indicated that toe-in gait lowered KAAI only in healthy individuals ($P = 0.02$) but not in individuals with knee OA ($P = 0.79$). There was a marginally significant effect of toe-in gait on KAAI between healthy individuals or individuals with knee OA ($\chi^2 = 3.95$, $P = 0.05$). Healthy individuals of normal weight did not experience a lower KAAI with toe-in gait ($P = 0.14$) (see Supplementary Table 2

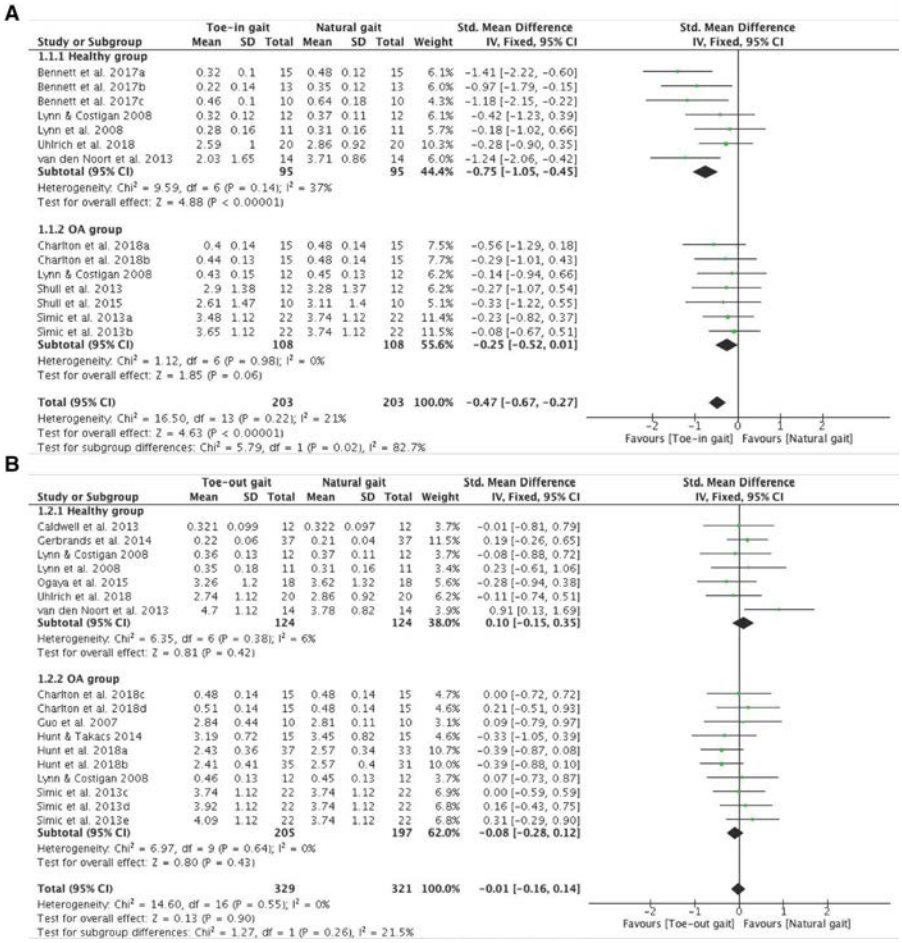

Figure 2. Forest plots for the effect of toe-in gait (**A**) and toe-out gait (**B**) on the first external knee adduction moment peak. Lower-case letters a, b, c, d, and e indicate comparisons between foot progression conditions within the same study. Diamonds represent the overall effect estimate; circles represent the effect estimate and weight for each study. 95% CI = 95% confidence interval; IV = inverse variance; OA = osteoarthritis.

and Supplementary Figure 7, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24420/abstract). Each knee alignment subgroup in healthy individuals did not show a significant effect of toe-in gait on KAAI ($P > 0.22$) (see Supplementary Table 2 and Supplementary Figure 7, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24420/abstract).

Toe-out gait significantly reduced KAAI (Figure 4B). Subgroup comparisons indicated that toe-out gait did not affect KAAI in healthy individuals ($P = 0.11$). Toe-out gait reduced KAAI in the knee OA group ($P = 0.03$) except for those with knee valgus alignment ($P = 0.81$) (see Supplementary Table 2 and Supplementary Figure 8, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24420/abstract).

DISCUSSION

To the best of our knowledge, this is the first meta-analysis to analyze the effects of FPA modification during walking on the EKAM peaks and KAAI between healthy individuals and patients with knee OA. We found that toe-in gait reduced the first EKAM peak but increased the second EKAM peak; and toe-out gait reduced the second EKAM peak and KAAI. The subgroup effects of FPA modification were inconsistent. For healthy individuals, toe-in gait lowered the first EKAM peak and KAAI, and toe-out gait reduced the second EKAM peak. For patients with knee OA, toe-out gait was found to reduce the second EKAM peak and KAAI, whereas toe-in gait did not affect EKAM or KAAI. Age, BMI, and knee alignment might also affect the outcome of FPA modification.

Regarding toe-in gait modification, we found a significant reduction in the first EKAM peak. Subgroup analysis revealed that such an effect was only observed in healthy individuals but not in patients with knee OA. The discrepancy might be because patients with knee OA had limited FPA range during toe-in gait (21). For example, the maximum FPA was only 9.7 ± 3.3° in the patient group (21), whereas it could reach 17.4 ± 4.6° for healthy individuals (14) in the included studies. To achieve any positive biomechanical effects of toe-in gait, FPA modification was expected to be at least 5° (25,26). Patients with knee OA, especially those with K/L grade IV, may have difficulty in exceeding

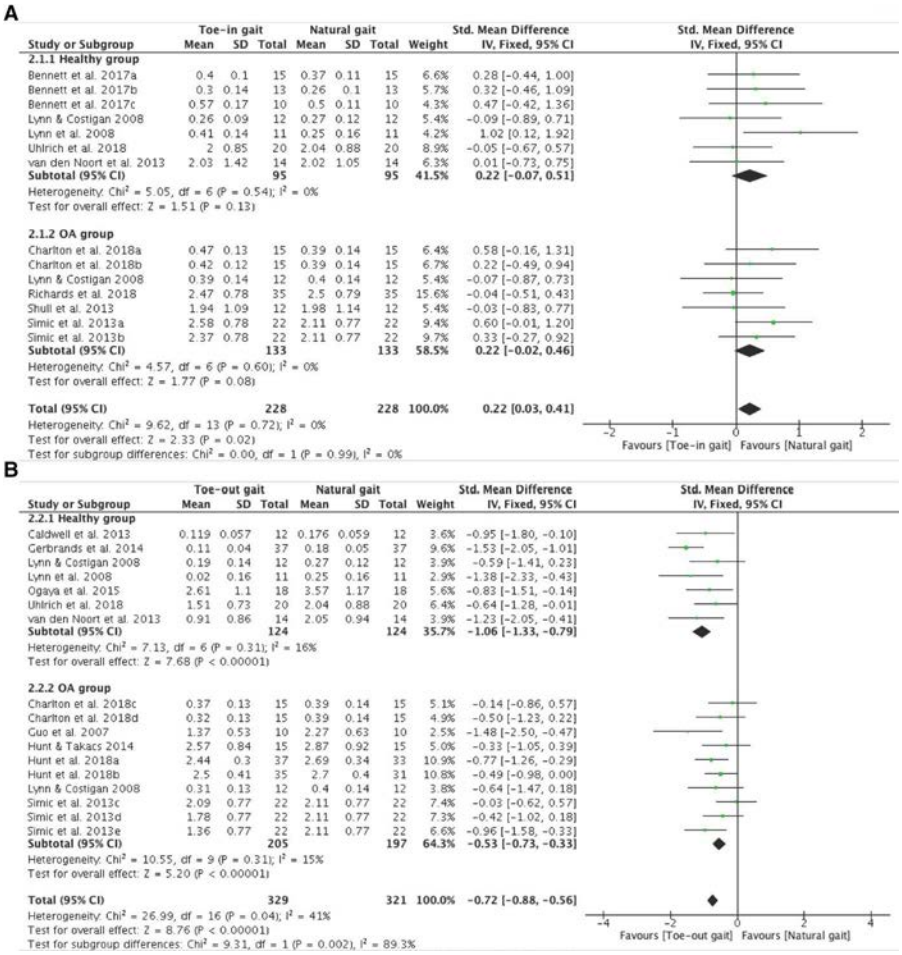

Figure 3. Forest plots for the effect of toe-in gait (**A**) and toe-out gait (**B**) on the second external knee adduction moment peak. Lower-case letters a, b, c, d, and e indicate comparisons between foot progression conditions within the same study. Diamonds represent the overall effect estimate; circles represent the effect estimate and weight for each study. 95% CI = 95% confidence interval; IV = inverse variance; OA = osteoarthritis.

that threshold. For example, patients with knee OA from included studies (16,21,25,26) exhibited an FPA of <5° during toe-in gait. Step width may be another factor to alter the effects of toe-in gait between individuals with and without knee OA. Healthy individuals are more likely to walk with greater step width than patients with knee OA (11). The first EKAM peak of patients with knee OA was found to be reduced with wider step width (44). Compared with natural gait, toe-in gait together with wider step was found to reduce the first EKAM peak in healthy individuals (45). Adjusting step width would compromise balance, which may be a problem for elderly individuals. We therefore only included studies investigating the effects of FPA modification, which is a subtler strategy for reducing EKAM than step width adjustment. The confounding effects of step width on EKAM and KAAI with FPA modification should be further studied.

Similar to previous studies (27,46), we found that toe-in gait increased the second EKAM peak; however, subgroup analysis revealed no significant differences in both healthy and knee OA groups. This might be because the overall effect size was small, whereas variances were great and sample size was relatively small for each subgroup (95 healthy individuals and 133 patients with knee OA). We found that toe-in gait reduced the KAAI in only the healthy group with an effect size of –0.46, which could be partially explained by the fact that the healthy group reduced the first EKAM peak and maintained the second EKAM peak, but EKAM remained similar in the knee OA group during toe-in gait modification. Another factor that can contribute to the observed differences is a longer stance in patients with knee OA compared to healthy individuals (45). It remains unknown whether there are differences in the stance duration between natural walking and toe-in gait.

Toe-out gait did not affect the first EKAM peak but significantly reduced the second EKAM peak in both healthy individuals (large effect size) and patients with knee OA (medium effect size). These could be explained by the reduction of EKAM lever arm, as the center of pressure shifts laterally during late stance (28). The clinical significance of the second EKAM peak is less well recognized than the first peak, and the reduction of the second EKAM peak may result in the reduction of KAAI (34). Our pooled results indicated that KAAI was reduced by toe-out gait. However,

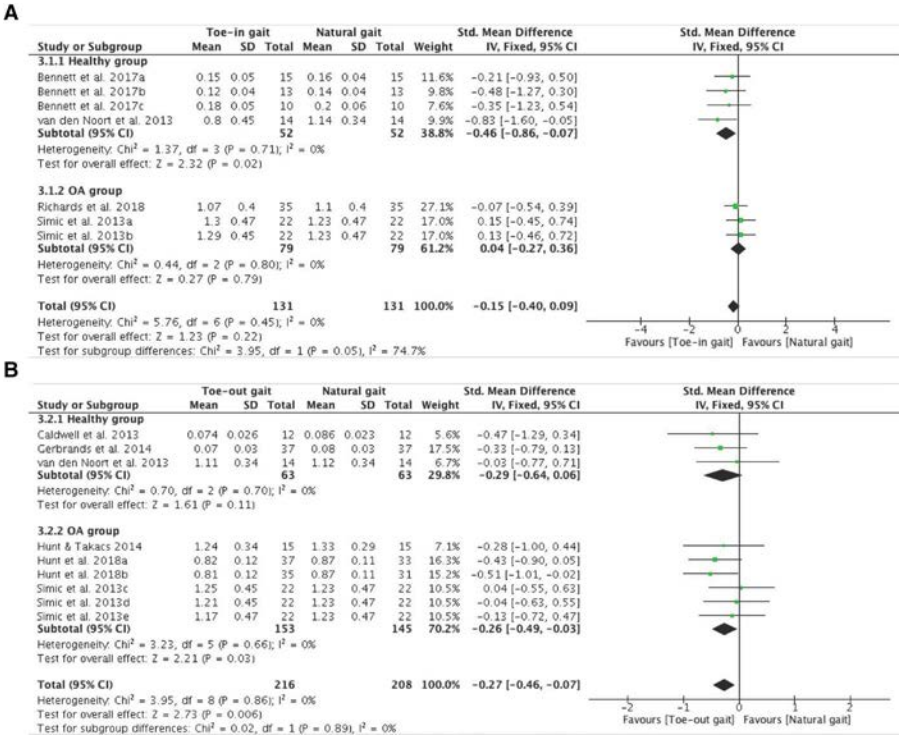

Figure 4. Forest plots for the effect of toe-in gait (**A**) and toe-out gait (**B**) on the knee adduction angular impulse. Lower-case letters a, b, c, d, and e indicate comparisons between foot progression conditions within the same study. Diamonds represent the overall effect estimate; circles represent the effect estimate and weight for each study. 95% CI = 95% confidence interval; IV = inverse variance; OA = osteoarthritis.

our subgroup analysis found that KAAI was only reduced in the knee OA group with a small effect. According to van den Noort et al (29), reduction of the second EKAM peak is usually accompanied by the increase of the first EKAM peak in healthy individuals, which may neutralize the effect of toe-out gait on KAAI. Toe-out gait may slow down knee OA progression, potentially due to its effect on the second EKAM peak and KAAI (47). Similar with previous findings (19,20), we found that toe-out gait reduced the second EKAM peak and KAAI in patients with knee OA; more importantly, reduction of EKAM and KAAI was associated with improved symptoms. Hunt et al stated that 10-week toe-out gait retraining alleviated knee pain by lowering the second EKAM peak in patients with knee OA (20). Although Hunt et al reported that both toe-out gait and walking exercise improved knee pain and function, only toe-out gait modification led to a reduction of the second EKAM peak and KAAI after 4 months of training (19). Therefore, the improved symptoms following the toe-out gait modification training program may be a result of walking exercise rather than the altered FPA (48).

Given the different effects of FPA modification on EKAM and KAAI between individuals with and without knee OA, FPA modification should be subject specific. For healthy individuals, toe-in gait would significantly reduce the first EKAM peak and KAAI when compared with natural walking, which may alleviate knee joint load. However, it does not mean that toe-out/neutral gait may increase the risk of knee OA in healthy individuals. To date, no prospective study has established a causal relationship between FPA and knee OA development. Regarding the effect of age, BMI, and knee alignment on EKAM and KAAI in our subgroup analyses, different results were detected on the first EKAM peak in elderly individuals (n = 12; mean ± SD age 68.7 ± 8.4 years) and KAAI in healthy individuals with normal weight (n = 38) or different knee alignments (n ≤ 15). However, we suggest interpreting these findings with caution, as the sample size was small, and data were extracted from the same study, which did not control for other confounding factors in the experiment.

For patients with knee OA, toe-out gait may be advocated to lower EKAM and KAAI during walking. Patients with knee OA were reported to naturally walk with FPA from 2.2° toe-in to 28.4° toe-out (average = 11.4° toe-out) (49). In previous patient-cohort studies, FPA was altered from 4.4° toe-in (21) to 18.6° toe-out (18). Moreover, different criteria were adopted to set the FPA target, e.g., 10° toe-out (20), 10° and 20° toe-out (2 targets) (16), and self-selected toe-out angle (17). It remains unknown how much the patients with knee OA should walk with toe out to achieve dose-response effects. Biofeedback gait retraining that offers real-time EKAM and/or KAAI data may provide subject-specific information for gait modifications (12,44), which might be an appropriate way for tailoring FPA modification training. Future studies should address that in clinical practice.

Prescription of toe-out gait for patients with knee OA is still arguable. Only 59% of patients with mild-to-moderate knee OA

exhibited a definitive second EKAM peak (50), and only <30% of patients with severe knee OA exhibited a definitive second EKAM peak (50). Toe-out gait was found to be related to an increased duration and magnitude of EKAM from initial to midstance (50), which could be detrimental to the knee joint, but it improved symptoms in patients with knee OA (19,20). Future studies should examine the relationship between toe-out gait and EKAM through waveform analytical techniques in combination with discrete measures (31,50).

We only observed marginal publication bias in studies investigating toe-in gait on the first EKAM peak. Publication bias was not present during subgroup analysis, which can be explained by the high heterogeneity between the healthy and knee OA groups ($\chi^2 = 7.30$, $P = 0.007$). Therefore, the effect of toe-in gait on the first EKAM peak in the knee OA group should be interpreted with caution.

There are some limitations to this meta-analysis. We did not have sufficient data to link FPA modification with progression of knee OA, as past studies only had a relatively short follow-up period. Our findings were mainly based on cross-sectional studies investigating patients with mild-to-severe knee OA. Both gait retraining programs and walking exercise may improve symptoms for patients with knee OA (48). Randomized controlled trials with long-term follow-up are warranted to better understand the relationship between changes in reported symptoms and knee loading reduction following a gait retraining program in a wider patient spectrum (i.e., all 4 K/L grades).

In conclusion, compared with natural walking, both toe-in and toe-out gait may be more effective in lowering EKAM and KAAI in healthy individuals. In contrast, toe-out gait may reduce EKAM and KAAI in patients with mild-to-severe knee OA. There are insufficient data from patients with early-stage knee OA, indicating that future research is required.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Cheung had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Wang, Cheung.

Acquisition of data. Wang, Mo, Cheung.

Analysis and interpretation of data. Wang, Mo, Chung, Shull, Ribeiro, Cheung.

REFERENCES

1. Garnero P, Piperno M, Gineyts E, Christgau S, Delmas PD, Vignon E. Cross sectional evaluation of biochemical markers of bone, cartilage, and synovial tissue metabolism in patients with knee osteoarthritis: relations with disease activity and joint damage. Ann Rheum Dis 2001;60:619–26.
2. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019;393:1745–59.
3. Mündermann A, Dyrby CO, D'Lima DD, Colwell CW, Andriacchi TP. In vivo knee loading characteristics during activities of daily living as measured by an instrumented total knee replacement. J Orthop Res 2008;26:1167–72.
4. Foroughi N, Smith R, Vanwanseele B. The association of external knee adduction moment with biomechanical variables in osteoarthritis: a systematic review. Knee 2009;16:303–9.
5. Hurwitz DE, Ryals AB, Case JP, Block JA, Andriacchi TP. The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain. J Orthop Res 2002;20:101–7.
6. Mündermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. Arthritis Rheum 2005;52:2835–44.
7. Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis 2002;61:617–22.
8. Maleki M, Arazpour M, Joghtaei M, Hutchins SW, Aboutorabi A, Pouyan A. The effect of knee orthoses on gait parameters in medial knee compartment osteoarthritis: a literature review. Prosthet Orthot Int 2016;40:193–201.
9. Petersen W, Ellermann A, Zantop T, Rembitzki IV, Semsch H, Liebau C, et al. Biomechanical effect of unloader braces for medial osteoarthritis of the knee: a systematic review (CRD 42015026136). Arch Orthop Trauma Surg 2016;136:649–56.
10. Felson DT, Parkes M, Carter S, Liu A, Callaghan MJ, Hodgson R, et al. The efficacy of a lateral wedge insole for painful medial knee osteoarthritis after prescreening: a randomized clinical trial. Arthritis Rheumatol 2019;71:908–15.
11. Hinman RS, Bowles KA, Metcalf BB, Wrigley TV, Bennell KL. Lateral wedge insoles for medial knee osteoarthritis: effects on lower limb frontal plane biomechanics. Clin Biomech (Bristol, Avon) 2012;27:27–33.
12. Cheung RT, Ho KK, Au IP, An WW, Zhang JH, Chan ZY, et al. Immediate and short-term effects of gait retraining on the knee joint moments and symptoms in patients with early tibiofemoral joint osteoarthritis: a randomized controlled trial. Osteoarthritis Cartilage 2018;26:1479–86.
13. Gerbrands TA, Pisters MF, Theeven PJ, Verschueren S, Vanwanseele B. Lateral trunk lean and medializing the knee as gait strategies for knee osteoarthritis. Gait Posture 2017;51:247–53.
14. Bennett HJ, Shen G, Cates HE, Zhang S. Effects of toe-in and toe-in with wider step width on level walking knee biomechanics in varus, valgus, and neutral knee alignments. Knee 2017;24:1326–34.
15. Caldwell LK, Laubach LL, Barrios JA. Effect of specific gait modifications on medial knee loading, metabolic cost and perception of task difficulty. Clin Biomech (Bristol, Avon) 2013;28:649–54.
16. Charlton JM, Hatfield GL, Guenette JA, Hunt MA. Ankle joint and rearfoot biomechanics during toe-in and toe-out walking in people with medial compartment knee osteoarthritis. PM R 2019;11:503–11.
17. Gerbrands TA, Pisters MF, Vanwanseele B. Individual selection of gait retraining strategies is essential to optimally reduce medial knee load during gait. Clin Biomech (Bristol, Avon) 2014;29:828–34.
18. Guo M, Axe MJ, Manal K. The influence of foot progression angle on the knee adduction moment during walking and stair climbing in pain free individuals with knee osteoarthritis. Gait Posture 2007;26:436–41.
19. Hunt MA, Charlton JM, Krowchuk NM, Tse CT, Hatfield GL. Clinical and biomechanical changes following a 4-month toe-out gait

modification program for people with medial knee osteoarthritis: a randomized controlled trial. Osteoarthritis Cartilage 2018;26:903–11.
20. Hunt MA, Takacs J. Effects of a 10-week toe-out gait modification intervention in people with medial knee osteoarthritis: a pilot, feasibility study. Osteoarthritis Cartilage 2014;22:904–11.
21. Lynn SK, Costigan PA. Effect of foot rotation on knee kinetics and hamstring activation in older adults with and without signs of knee osteoarthritis. Clin Biomech (Bristol, Avon) 2008;23:779–86.
22. Lynn SK, Kajaks T, Costigan PA. The effect of internal and external foot rotation on the adduction moment and lateral-medial shear force at the knee during gait. J Sci Med Sport 2008;11:444–51.
23. Ogaya S, Naito H, Iwata A, Higuchi Y, Fuchioka S, Tanaka M. Toe-out gait decreases the second peak of the medial knee contact force. J Appl Biomech 2015;31:275–80.
24. Richards RE, Andersen MS, Harlaar J, van den Noort JC. Relationship between knee joint contact forces and external knee joint moments in patients with medial knee osteoarthritis: effects of gait modifications. Osteoarthritis Cartilage 2018;26:1203–14.
25. Shull PB, Huang Y, Schlotman T, Reinbolt JA. Muscle force modification strategies are not consistent for gait retraining to reduce the knee adduction moment in individuals with knee osteoarthritis. J Biomech 2015;48:3163–9.
26. Shull PB, Shultz R, Silder A, Dragoo JL, Besier TF, Cutkosky MR, et al. Toe-in gait reduces the first peak knee adduction moment in patients with medial compartment knee osteoarthritis. J Biomech 2013;46:122–8.
27. Simic M, Wrigley TV, Hinman RS, Hunt MA, Bennell KL. Altering foot progression angle in people with medial knee osteoarthritis: the effects of varying toe-in and toe-out angles are mediated by pain and malalignment. Osteoarthritis Cartilage 2013;21:1272–80.
28. Uhlrich SD, Silder A, Beaupre GS, Shull PB, Delp SL. Subject-specific toe-in or toe-out gait modifications reduce the larger knee adduction moment peak more than a non-personalized approach. J Biomech 2018;66:103–10.
29. Van den Noort JC, Schaffers I, Snijders J, Harlaar J. The effectiveness of voluntary modifications of gait pattern to reduce the knee adduction moment. Hum Mov Sci 2013;32:412–24.
30. Richards RE, van den Noort JC, van der Esch M, Booij MJ, Harlaar J. Effect of real-time biofeedback on peak knee adduction moment in patients with medial knee osteoarthritis: is direct feedback effective? Clin Biomech (Bristol, Avon) 2018;57:150–8.
31. Thorp LE, Wimmer MA, Block JA, Moisio KC, Shott S, Goker B, et al. Bone mineral density in the proximal tibia varies as a function of static alignment and knee adduction angular momentum in individuals with medial knee osteoarthritis. Bone 2006;39:1116–22.
32. Bennell KL, Bowles KA, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis 2011;70:1770–74.
33. Simic M, Hinman RS, Wrigley TV, Bennell KL, Hunt MA. Gait modification strategies for altering medial knee joint load: a systematic review. Arthritis Care Res (Hoboken) 2011;63:405–26.
34. Richards R, van den Noort JC, Dekker J, Harlaar J. Gait retraining with real-time biofeedback to reduce knee adduction moment: systematic review of effects and methods used. Arch Phys Med Rehabil 2017;98:137–50.
35. Draganich LF, Kuo CE. The effects of walking speed on obstacle crossing in healthy young and healthy older adults. J Biomech 2004;37:889–96.
36. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum 2005;52:2026–32.
37. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Chinese Integr Med 2009;7:889–96.
38. Shaw KE, Charlton JM, Perry CK, de Vries CM, Redekopp MJ, White JA, et al. The effects of shoe-worn insoles on gait biomechanics in people with knee osteoarthritis: a systematic review and meta-analysis. Br J Sports Med 2018;52:238–53.
39. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377–84.
40. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. Health Technol Assess 2003;7:iii–x.
41. Cohen J. A power primer. Psychol Bull 1992;112:155–9.
42. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
43. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
44. Fregly BJ. Computational assessment of combinations of gait modifications for knee osteoarthritis rehabilitation. IEEE Trans Biomed Eng 2008;55:2104–6.
45. Favre J, Erhart-Hledik JC, Chehab EF, Andriacchi TP. General scheme to reduce the knee adduction moment by modifying a combination of gait variables. J Orthop Res 2016;34:1547–56.
46. Khan SS, Khan SJ, Usman J. Effects of toe-out and toe-in gait with varying walking speeds on knee joint mechanics and lower limb energetics. Gait Posture 2017;53:185–92.
47. Chang A, Hurwitz D, Dunlop D, Song J, Cahue S, Hayes K, et al. The relationship between toe-out angle during gait and progression of medial tibiofemoral osteoarthritis. Ann Rheum Dis 2007;66:1271–5.
48. Ettinger WH, Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis: the fitness arthritis and seniors trial (FAST). JAMA 1997;277:25–31.
49. Jenkyn TR, Hunt MA, Jones IC, Giffin JR, Birmingham TB. Toe-out gait in patients with knee osteoarthritis partially transforms external knee adduction moment into flexion moment during early stance phase of gait: a tri-planar kinetic mechanism. J Biomech 2008;41:276–83.
50. Rutherford DJ, Hubley-Kozey CL, Deluzio KJ, Stanish WD, Dunbar M. Foot progression angle and the knee adduction moment: a cross-sectional investigation in knee osteoarthritis. Osteoarthritis Cartilage 2008;16:883–9.

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Examining the Association of Knee Pain With Modifiable Cardiometabolic Risk Factors

Daniel A. Charen,[1] David Solomon,[2] Nicole Zubizarreta,[1] Jashvant Poeran,[1] and Alexis C. Colvin[1]

Objective. A well-established link exists between obesity and knee osteoarthritis, and recent research has implicated diabetes mellitus as a potential cause of cartilage degeneration. The objective of this study was to use the National Health and Nutrition Examination Survey (NHANES) database to examine the association between knee pain and various metabolic factors.

Methods. A retrospective cross-sectional study of the NHANES database from 1999 to 2004 was performed. The main outcome was any knee pain and bilateral knee pain. The main effects of interest were body mass index (BMI) and glycohemoglobin A_{1c}. We additionally assessed various patient factors, including age, race, poverty, sex, and smoking status. Multivariable logistic regression models and interaction terms were analyzed.

Results. Data on 12,900 patients were included. In the main adjusted analysis, the modifiable risk factors associated with any knee pain were overweight (odds ratio [OR] 0.91 [95% confidence interval (95% CI) 0.85–0.97), obesity (OR 1.54 [95% CI 1.42–1.66]), glycemic control (OR 1.20 [95% CI 1.03–1.38]), and current smoking (OR 1.15 [95% CI 1.05–1.27]) (all $P < 0.05$). These same factors remain significant for bilateral knee pain. Subgroup analysis showed that patients age <65 years have a 5% increase in the risk of any knee pain as their BMI increases, but patients age ≥65 years have a 10% increase in risk.

Conclusion. This study confirms the association of knee pain with increased weight, glycemic control, current smoking, and age. Most of these risk factors can be modified in patients with knee pain and should be discussed when providing conservative treatment options.

INTRODUCTION

Rates of obesity and diabetes mellitus have been sharply rising in the US over the past several decades (1). In 2015, the Centers for Disease Control estimated that 30.3 million Americans were living with diabetes mellitus, representing 9.4% of the population (2). There is a well-established link between obesity and knee osteoarthritis, and recent research has implicated diabetes mellitus and hyperglycemia as a potential cause of cartilage degeneration (3–5). Other medical conditions associated with knee pain include hypertension and dyslipidemia (6–8). Possible explanations for these associations include the effects of increased force transmission through weight-bearing joints (9–15) and endocrine system changes such as changes in leptin, adiponectin, and other adipokines (16,17).

The National Health and Nutrition Examination Survey (NHANES) database has been widely studied to examine the relationship between knee osteoarthritis and cardiometabolic risk factors, such as obesity and diabetes mellitus. Prior NHANES studies, including NHANES I and III, were used to explore the relationship between degenerative knee changes on radiographs and cardiometabolic risk factors, demonstrating an association with increased body mass index (BMI) (18), leptin, and female sex (16,19). However, to what extent these factors are associated with knee pain rather than radiographic degenerative changes is unknown. Making the distinction between the presence of osteoarthritis on radiographs and the presence of knee pain is important. A prior study demonstrated that 50% of people in the general population with radiographic findings of knee osteoarthritis do not have pain, and 50% of people with knee pain age >54 years do not have radiographic findings of osteoarthritis (20).

The goal of this study was to examine the relationship between modifiable cardiometabolic risk factors (obesity, glycohemoglobin A_{1c} [HbA_{1c}], and smoking) and self-reported knee pain, which differs from previous studies that examined patients with degenerative changes seen on radiographs. Our study design will

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- Obesity, glycemic control, and current smoking status are significant modifiable risk factors for knee pain.
- Patients age <65 years have a 5% increase in risk of any knee pain as their body mass index increases, but patients age ≥65 years have a 10% increase in risk.
- Modification of these modifiable risk factors in patients with knee pain is a valuable tool for physicians when discussing conservative treatment options.

be more representative of the total knee pain cohort rather than a focus on those individuals with degenerative joint disease. An additional objective was to determine whether there were different risk factors in patients with bilateral knee pain compared to unilateral knee pain.

MATERIALS AND METHODS

Study design and cohort. This retrospective cross-sectional study used data from the NHANES database created by the Centers for Disease Control and Prevention's National Center for Health Statistics (21). It is a nationally representative sample of the US residential population composed of noninstitutionalized civilians. The surveys provide a comprehensive look into an individual's demographic information, health, and nutritional and household status. Also, there is a collection of blood and urine for laboratory testing. Data for the current study came from 3 different NHANES cycles (1999–2000, 2001–2002, 2003–2004) because these had a specialized questionnaire about pain. The Institutional Review Board at the Icahn School of Medicine at Mount Sinai deemed the use of these anonymized data for research as exempt from a full review (HS#19-00876).

Study variables. The primary outcome for this study was any (unilateral or bilateral) knee pain as captured by the NHANES Miscellaneous Pain Questionnaire. Here, participants were asked to circle the joints that caused them pain on a sheet of paper; thus, a participant could identify whether they had unilateral or bilateral knee pain. The main variables of interest were BMI, HbA_{1c}, and smoking status. We decided not to include knee radiograph analysis of these patients since such analysis had been performed in prior studies and was not the focus of this article (16,18,19).

The cohort included any participant age >20 years who had all of the following: HbA_{1c} measurement, BMI calculation, and completion of pain questionnaire. HbA_{1c} came from the laboratory data and was used to determine glycemic control using a threshold of ≥6.5% for HbA_{1c} (22). An additional exclusion criterion was anyone with a BMI of <18.5, considered to be underweight. Based on the World Health Organization guidelines for BMI and nutritional status, people were categorized as normal weight, overweight, and obese (23). Additional demographic variables were age, race (White, Black, Hispanic, other), sex, and family poverty:income ratio (PIR). The PIR can be used as a proxy for socioeconomic status, and a PIR ranges from 0 to 5, with a PIR of <1 representing below poverty level. Smoking status was assessed in 2 steps: first if the patient answered "Smoked at least 100 cigarettes in life," then if the patient currently smoked cigarettes. Based on this information, participants were classified as never smokers, former smokers, and current smokers.

Statistical analysis. The cohort was described using the median and interquartile range for continuous variables and absolute numbers for categorical variables. Also, the weighted percentage of participants with any knee pain was reported for each categorical variable. A multivariable logistic regression model was performed to determine an association between any knee pain adjusting for the following covariates: age, PIR, race, glycemic control, BMI/weight category, smoking status, and sex. We tested for potential multicollinearity specifically between BMI and HbA_{1c} using variance inflation factors (VIF) prior to any modeling; all VIF values were <10, indicating no issue with multicollinearity. Odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) are reported. Using interaction terms in the main model between the modifiable risk factors and other covariates, we were able to identify potential subgroup analyses. We then performed subgroup analyses for race, BMI/weight category, sex, and age, adjusting for the same covariates as the main model. We graphed the proportion of patients with any knee pain by age to determine an inflection point.

To evaluate the robustness of our results, we decided to look at bilateral knee pain. This cohort is made up of anyone with at least unilateral knee pain. Bilateral knee pain was defined if a participant circled both knees as causing them pain in the NHANES Miscellaneous Pain Questionnaire. The same analysis was done for this outcome and adjusting for the same covariates. The only subgroup analysis performed was for age. Statistical significance was determined at P value less than 0.05. Sampling weights were used in all the descriptive and multivariable analyses as specified by NHANES guidelines (24). All analyses were performed using SAS statistical software, version 9.4.

RESULTS

Of 12,900 participants surveyed, 3,144 (24.4%) reported any knee pain. Participants with knee pain (compared to those without knee pain) tended to be older, have a lower PIR with a slightly higher BMI and elevated HbA_{1c}, and were more often female, White, obese, and former smokers (Table 1). Of the 3,144 participants with knee pain, 1,816 (56.8% weighted proportion) had bilateral knee pain. The same associations held true for

Table 1. Knee pain by study variables*

Variable	All	Any knee pain			Bilateral knee pain		
		Pain	No pain	%	Pain	No pain	%
Total number	12,900	3,144	9,756	24.8	1,816	11,084	14.1
Age, years	43.9 (32.3–56.7)	48.3 (37.3–60.8)	42.3 (31.1–55.0)	–	50.2 (38.9–62.7)	42.9 (31.5–55.6)	–
Sex, no.							
Male	6,137	1,397	4,740	23.2	747	5,390	12.1
Female	6,763	1,747	5,016	26.4	1,069	5,694	15.9
Race, no.							
White	6,483	1,713	4,770	26.1	1,000	5,483	15.0
Black	2,402	596	1,806	24.4	317	2,085	13.0
Hispanic	3,559	742	2,817	19.5	441	3,118	10.9
Other	456	93	363	20.4	58	398	12.3
Poverty:income ratio	3.0 (1.5–5.0)	2.7 (1.4–4.7)	3.1 (1.6–5.0)	–	2.7 (1.3–4.4)	3.1 (1.6–5.0)	–
Body mass index, kg/m^2	27.2 (23.9–31.3)	28.7 (25.0–33.6)	26.8 (23.6–30.6)	–	29.0 (25.1–34.1)	26.9 (23.8–30.8)	–
Weight group, no.							
Normal	3,969	725	3,244	18.8	407	3,562	10.4
Overweight	4,726	1,083	3,643	22.9	800	3,405	19.9
Obese	4,205	1,336	2,869	33.3	609	4,117	12.5
HbA_{1c}	5.3 (5.0–5.5)	5.3 (5.1–5.6)	5.2 (5.0–5.5)	–	5.3 (5.1–5.7)	5.2 (5.0–5.5)	–
Glycemic control (HbA_{1c}), no.							
<5.7%	9,569	2,102	7,467	23.1	1,158	8,411	12.6
5.7–6.4%	2,169	660	1,509	29.8	407	1,762	18.9
≥6.5%	1,162	382	780	35.8	251	911	23.5
Smoking status, no.							
Current	2,768	684	2,084	25.5	392	2,376	14.8
Former	3,467	952	2,515	27.0	564	2,903	15.8
Never	6,665	1,508	5,157	23.3	860	5,805	12.9

* Values are the median (interquartile range) unless indicated otherwise. Modifiable cardiometabolic risk factors include body mass index, weight group, glycohemoglobin A_{1c} (HbA_{1c}), glycemic control, and smoking status. Values show unweighted number, weighted %.

participants for bilateral knee pain, except that participants who were overweight had more bilateral knee pain than those who were obese.

Based on the full model, the modifiable risk factors significantly associated with higher odds of any knee pain were obesity (OR 1.54 [95% CI 1.42–1.66]), glycemic control (OR 1.20 [95% CI 1.03–1.38]), and current smoking (OR 1.15 [95% CI 1.05–1.27]), all $P < 0.05$ (Table 2). Compared to participants of normal weight, participants who were overweight had lower odds of any knee pain (OR 0.91 [95% CI 0.85–0.97]). The full model for bilateral knee pain showed similar results, except that being overweight was no longer significant.

Using the interaction terms, it generated subgroup analyses for race, BMI/weight category, sex, and age for any knee pain (Table 3). Age was dichotomized by looking at the inflection point when age was plotted against the proportion with knee pain, which was determined to be age 65 years (Figure 1). As BMI increased, participants age ≥65 years still had almost double the risk of bilateral knee pain compared to those individuals who were younger

Table 2. Results from multivariable models showing odds ratios (ORs) for modifiable cardiometabolic risk factors*

Risk factor	Any knee pain		Bilateral knee pain	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Weight group				
Normal	Ref.	–	Ref.	–
Overweight	0.91 (0.85–0.97)	0.0087	0.90 (0.80–1.00)	0.0582
Obese	1.54 (1.42–1.66)	<0.0001	1.53 (1.39–1.69)	<0.0001
Glycemic control (HbA_{1c})				
<5.7%	Ref.	–	Ref.	–
5.7–6.4%	0.88 (0.78–1.00)	0.0528	0.91 (0.81–1.02)	0.1078
>6.5%	1.20 (1.03–1.38)	0.0167	1.27 (1.09–1.49)	0.0027
Smoking status				
Never	Ref.	–	Ref.	–
Current	1.15 (1.05–1.27)	0.0051	1.20 (1.07–1.35)	0.0024
Former	0.96 (0.88–1.04)	0.2905	0.98 (0.89–1.08)	0.6874

* Model adjusted for age, sex, race, poverty:income ratio, weight group, glycohemoglobin A_{1c} (HbA_{1c}) group, and smoking status. 95% CI = 95% confidence interval; Ref. = reference.

Table 3. Results from multivariable models by subgroups*

	Odds ratio (95% CI)	*P*
Any knee pain		
HbA_{1c}		
Race		
White	1.06 (0.97–1.15)	0.2194
Black	0.95 (0.86–1.06)	0.3704
Hispanic	0.95 (0.86–1.05)	0.2999
Other	1.15 (1.00–1.31)	0.0485
Weight group		
Normal weight	0.94 (0.82–1.08)	0.3906
Overweight	1.04 (0.95–1.15)	0.3947
Obese	0.94 (0.82–1.08)	0.1776
Sex		
Male	0.99 (0.92–1.06)	0.7261
Female	1.08 (0.99–1.18)	0.0966
Body mass index		
Age <65 years	1.05 (1.04–1.06)	<0.0001
Age ≥65 years	1.09 (1.07–1.11)	<0.0001
Cigarette smoker		
Never	Ref.	–
Current		
Age <65 years	1.11 (0.99–1.23)	0.0687
Age ≥65 years	1.06 (0.85–1.32)	0.5880
Former		
Age <65 years	1.04 (0.94–1.15)	0.4104
Age ≥65 years	0.97 (0.84–1.11)	0.6350
Bilateral knee pain		
Body mass index		
Age <65 years	1.05 (1.04–1.06)	<0.0001
Age ≥65 years	1.08 (1.07–1.10)	<0.0001

* Model adjusted for age, sex, race, poverty:income ratio, weight group, glycohemoglobin A_{1c} (HbA_{1c}) group, and smoking status. 95% CI = 95% confidence interval; Ref. = reference.

(*P* < 0.0001; OR 1.09 [95% CI 1.07–1.11] and OR 1.05 [95% CI 1.04–1.06], respectively). For bilateral pain, the only subgroup analysis was for age and by using the graphical approach, age 65 years was again used as the cutoff point. Participants age ≥65 years still had almost double the risk of bilateral knee pain compared to those individuals who were younger when BMI increased.

DISCUSSION

This study demonstrates that risk factors for knee pain are older age, glycemic control, obesity, and current smoking. The significant association between knee pain and glycemic control, BMI, and smoking may be related to an increased prevalence of the metabolic subtype of osteoarthritis in these patients. This subtype is defined by the presence of metabolic syndrome, adipokines, hyperglycemia, hormonal imbalance, and the presence of metabolic subtypes of osteoarthritis in middle-aged people (9).

Metabolic syndrome is found in 59% of patients with osteoarthritis and in only 23% of patients without osteoarthritis (25). This syndrome is most commonly defined by insulin resistance, visceral obesity, atherogenic dyslipidemia, and hypertension (9). As the number of metabolic syndrome components increases, the severity of knee pain has been shown to increase (26). Metabolic syndrome and the metabolic subtype of osteoarthritis share mechanisms of oxidative stress, common metabolites, and endothelial dysfunction. This relationship was confirmed by a prior NHANES study, which demonstrated that hypertension, abdominal obesity, triglycerides, low high-density lipoprotein, and hyperglycemia were also associated with osteoarthritis (6). Our study confirmed the link between obesity and knee pain—although, interestingly, the overweight population actually had a decreased rate of any knee pain. Once a person reaches a certain BMI, however, the risk of knee pain seems to significantly increase.

Comparing patients with osteoarthritis and metabolic syndrome to those without metabolic syndrome, patients with metabolic syndrome develop osteoarthritis earlier and have more systemic pathology, increased inflammation, and increased joint pain (9). These findings are supported by Hannan et al, who demonstrated that there is a substantial discordance between knee pain and radiographic findings of knee osteoarthritis (27). Patients with metabolic syndrome may have worse knee pain despite relatively benign findings on radiographs. Behavior modification or

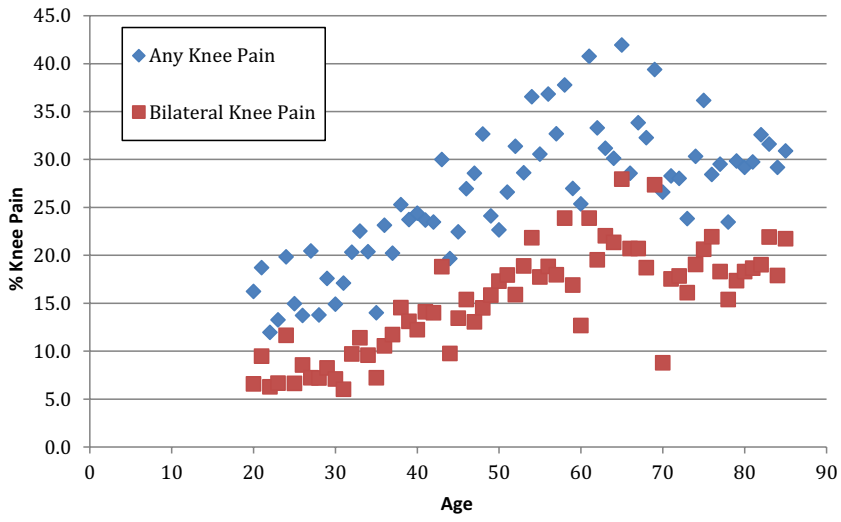

Figure 1. Trends in knee pain by age.

even aggressive weight loss management may be helpful in these patients. Üstün and colleagues demonstrated an improvement in knee pain after surgical weight loss (although this improvement did not correlate with weight loss amount), and there is currently an ongoing study evaluating the effectiveness of the antiobesity agent liraglutide for reduction of knee pain due to osteoarthritis (28,29).

The association of diabetes mellitus with knee osteoarthritis has been widely studied. Hyperglycemia leads to local accumulation of glycosylation end products, which can produce a toxic intraarticular environment (30–34). Type II collagen, which has low cell turnover, may be particularly affected by this glycosylation process (35). Local accumulation of glycosylation end products, may increase the stiffness of the cartilage collagen network, reducing its resistance to mechanical stress (36). The enhanced production of other inflammatory and degradative products due to hyperglycemia includes interleukin-6, matrix metalloproteinases, cyclooxygenase 2, and reactive oxygen species (37–39). This enhanced production may lead to cartilage degeneration and joint space narrowing, which is greater in patients with diabetes mellitus compared to individuals without diabetes mellitus (3). The results of these basic science studies are consistent with clinical findings that patients with noninsulin-dependent diabetes mellitus more often have bilateral knee or hip osteoarthritis, suggesting diabetes mellitus is a risk factor for osteoarthritis (40).

Several basic science studies have demonstrated detrimental intraarticular effects of other components of metabolic syndrome. Hypertension is linked to subchondral ischemia, which can compromise articular cartilage nutrient exchange (41–43). Furthermore, obesity-altered adipokine levels induce the expression of proinflammatory factors and degradative enzymes, inhibiting cartilage matrix synthesis and stimulating subchondral bone remodeling (44–49). These relationships are important, since osteoarthritis is the main source of knee pain in the general population, and studies of European patients have demonstrated the prevalence of musculoskeletal pain in the general population of up to 83% (50–53). Knee imaging studies have demonstrated a correlation of pain with synovitis and subchondral bone changes, such as bone marrow edema (54–56). Therefore, successful control of metabolic syndrome with medical management and lifestyle changes may improve knee pain and should be considered for future research.

That being said, Richey et al demonstrated that in individuals with established knee pain from osteoarthritis, intense lifestyle intervention did not alter progression to total knee arthroplasty compared to the control group of receiving standard diabetes mellitus support and education (57). However, a different study from the same trial demonstrated an improvement in knee pain symptoms and physical functioning at 1 year follow-up for patients in the intense lifestyle intervention group (58). Whether this improvement continues beyond this time is uncertain, since there is significant weight gain beyond 1 year (59).

In our study, the odds of any knee pain doubled above age 64 years. The aging process, although not a modifiable risk factor, is associated with changes to articular cartilage. As age increases, advanced glycation end products accumulate in articular cartilage. This accumulation has been demonstrated to increase cartilage brittleness and stiffness, as well as decreasing the synthesis and degradation of cartilage matrix constituents (60). A magnetic resonance imaging–based study showed that the most consistent knee structural changes with increasing age are an increase in cartilage defect severity and prevalence, cartilage thinning, and increasing bone size (61). The high rate of knee osteoarthritis in older individuals has been observed clinically as well. In a study of patients age >50 years with self reported knee pain, osteoarthritis was found in 77% of men and 61% of women (62).

This study demonstrated significant associations between knee pain and current smokers. Conflicting results have occurred in the literature as to whether smoking is a risk factor or protective for knee pain. Amin et al found that men who were current smokers were at increased risk for cartilage loss in the medial tibiofemoral joint (OR 2.3) and in the patellofemoral joint (OR 2.5) (63). Current smokers also had higher knee pain scores compared to men who were not current smokers. Possible explanations include a direct effect on intraarticular pain fibers or differences in socioeconomic status, which may influence how pain is perceived (64). Our study also demonstrated no significant association between knee pain and former smokers, which may imply that smoking cessation could improve knee pain and possibly even reverse the intraarticular effects of smoking. However, Sandmark et al showed that smokers were less likely to develop knee osteoarthritis and undergo total knee arthroplasty than nonsmokers (65). This lack of association may be due to smokers having a lower BMI, or to the fact that smokers have more medical comorbidities and are less likely to undergo total knee arthroplasty due to the increased risk. That being said, encouraging patients to undergo smoking cessation and providing the necessary resources may be a helpful adjunct in the conservative management of knee pain.

There are several limitations of this study. Since this was a large database study, we are only able to show correlation among variables and not causation. In addition, given that patients simply circled the entire knee joint on their pain survey, there was no way to determine the exact location of the knee pain, nature of the pain, or the source of pain. This etiology could include a myriad of etiologies, such as a traumatic meniscal tear, patellar tendonitis, inflammatory arthritis (i.e., gout), fracture, or degenerative joint disease. Although not the objective of this study, knee radiographs would have been helpful for determining the etiology of the pain. There was also no way to reliably link duration of pain with its location based on the database format; thus, even acute incidences of knee pain are likely included. This lack of specificity creates a highly heterogeneous group, which may limit our ability to draw conclusions. However, such variation may be partially addressed by using bilateral knee pain (as opposed to any knee pain) in our additional analysis, which is less likely to include acute pathology (66). Notably, differences in educational backgrounds and ethnicities may affect the reporting of how the survey questions about pain are interpreted.

One of the major strengths was the ability to include thousands of patients who are representative of the American population. Furthermore, NHANES is a heavily reviewed database with a validated methodology. Many different variables are studied, which allows for a comprehensive examination of a patient's metabolic and demographic status.

This study confirms the association of knee pain with the modifiable risk factors of obesity, glycemic control, and current smoking. In addition, the risk of knee pain doubles at age 65 years. Despite these associations, emphasis should still be placed on determining a biomechanical etiology for a patient's knee pain for guiding management. That being said, lifestyle modifications of weight loss, diabetes mellitus control, and smoking cessation may be useful adjuncts in the treatment regimens of physicians when providing conservative treatment options for patients.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Charen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Charen, Solomon, Zubizarreta, Poeran, Colvin.

Acquisition of data. Zubizarreta, Poeran.

Analysis and interpretation of data. Charen, Solomon, Zubizarreta, Poeran, Colvin.

REFERENCES

1. Nguyen US, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. Ann Intern Med 2011;155:725–32.
2. Centers for Disease Control and Prevention. National diabetes statistics report, 2017. Atlanta (GA): Centers for Disease Control and Prevention; 2017.
3. Eymard F, Parsons C, Edwards MH, Petit-Dop F, Reginster JY, Bruyère O, et al. Diabetes is a risk factor for knee osteoarthritis progression. Osteoarthritis Cartilage 2015;23:851–9.
4. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. J Rheumatol 1995;22:1118–23.
5. Cimmino MA, Cutolo M. Plasma glucose concentration in symptomatic osteoarthritis: a clinical and epidemiological survey. Clin Exp Rheumatol 1990;8:251–7.
6. Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. Postgrad Med 2009;121:9–20.
7. Lawrence JS. Hypertension in relation to musculoskeletal disorders. Ann Rheum Dis 1975;34:451–6.
8. Stürmer T, Sun YI, Sauerland S, Zeissig I, Günther KP, Puhl W, et al. Serum cholesterol and osteoarthritis: the baseline examination of the Ulm Osteoarthritis Study. J Rheumatol 1998;25:1827–32.
9. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. Nat Rev Rheumatol 2012;8:729–37.
10. Gabay O, Hall DJ, Berenbaum F, Henrotin Y, Sanchez C. Osteoarthritis and obesity: experimental models. Joint Bone Spine 2008;75:675–9.
11. Chowdhury TT, Arghandawi S, Brand J, Akanji OO, Bader DL, Salter DM, et al. Dynamic compression counteracts IL-1β induced inducible nitric oxide synthase and cyclo-oxygenase-2 expression in chondrocyte/agarose constructs. Arthritis Res Ther 2008;10:R35.
12. Gosset M, Berenbaum F, Levy A, Pigenet A, Thirion S, Saffar JL, et al. Prostaglandin E2 synthesis in cartilage explants under compression: mPGES-1 is a mechanosensitive gene. Arthritis Res Ther 2006;8:R135.
13. Gabay O, Gosset M, Levy A, Salvat C, Sanchez C, Pigenet A, et al. Stress-induced signaling pathways in hyalin chondrocytes: inhibition by avocado–soybean unsaponifiables (ASU). Osteoarthritis Cartilage 2008;16:373–84.
14. Fitzgerald JB, Jin M, Chai DH, Siparsky P, Fanning P, Grodzinsky AJ. Shear-and compression-induced chondrocyte transcription requires MAPK activation in cartilage explants. J Biol Chem 2008;283:6735–43.
15. Shimazaki A, Wright MO, Elliot K, Salter DM, Millward-Sadler SJ. Calcium/calmodulin-dependent protein kinase II in human articular chondrocytes. Biorheology 2006;43:223–33.
16. Karvonen-Gutierrez CA, Sowers MR, Heeringa SG. Sex dimorphism in the association of cardiometabolic characteristics and osteophytes-defined radiographic knee osteoarthritis among obese and non-obese adults: NHANES III. Osteoarthritis Cartilage 2012;20:614–21.
17. Conde J, Scotece M, Lopez V, Gomez R, Lago F, Pino J, et al. Adipokines: novel players in rheumatic diseases. Discov Med 2013;15:73–83.
18. Andersen RE, Crespo CJ, Bartlett SJ, Bathon JM, Fontaine KR. Relationship between body weight gain and significant knee, hip, and back pain in older Americans. Obes Res 2003;11:1159–62.
19. Newberry SJ, FitzGerald J, SooHoo NF, Booth M, Marks J, Motala A, et al. Treatment of osteoarthritis of the knee: an update review. Rockville (MD): Agency for Healthcare Research and Quality; 2017. Report No. 17-EHC011-EF.
20. McAlindon TE, Snow S, Cooper C, Dieppe PA. Radiographic patterns of osteoarthritis of the knee joint in the community: the importance of the patellofemoral joint. Ann Rheum Dis 1992;51:844–9.
21. Curtin LR, Mohadjer LK, Dohrmann SM, Montaquila JM, Kruszan-Moran D, Mirel LB, et al. The National Health and Nutrition Examination Survey: sample design, 1999–2006. Vital Health Stat 2 2012;155:1–39.
22. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2013;36 Suppl 1:S67–74.
23. World Health Organization. Body mass index: BMI. URL: www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi.
24. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey. Module 3: weighting. 2018. URL: wwwn.cdc.gov/nchs/nhanes/tutorials/module3.aspx.
25. Singh G, Miller JD, Lee FH, Pettitt D, Russell MW. Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. Am J Manag Care 2002;8 Suppl:S383–91.
26. Shin D. Association between metabolic syndrome, radiographic knee osteoarthritis, and intensity of knee pain: results of a national survey. J Clin Endocrinol Metab 2014;99:3177–83.
27. Hannan MT, Felson DT, Pincus TH. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol 2000;27:1513–7.
28. Üstün I, Solmaz A, Gülçiçek OB, Kara S, Albayrak R. Effects of bariatric surgery on knee osteoarthritis, knee pain and quality of life in female patients. J Musculoskelet Neuronal Interact 2019;19:465–71.
29. Gudbergsen H, Henriksen M, Wæhrens EE, Overgaard A, Bliddal H, Christensen R, et al. Protocol for a randomised, double-blind, placebo-controlled, parallel-group, single-centre trial. BMJ Open 2019;9:e024065.

30. McNulty AL, Stabler TV, Vail TP, McDaniel GE, Kraus VB. Dehydroascorbate transport in human chondrocytes is regulated by hypoxia and is a physiologically relevant source of ascorbic acid in the joint. Arthritis Rheum 2005;52:2676–85.
31. Henrotin YE, Bruckner P, Pujol JP. The role of reactive oxygen species in homeostasis and degradation of cartilage. Osteoarthritis Cartilage 2003;11:747–55.
32. Hiraiwa H, Sakai T, Mitsuyama H, Hamada T, Yamamoto R, Omachi T, et al. Inflammatory effect of advanced glycation end products on human meniscal cells from osteoarthritic knees. Inflamm Res 2011;60:1039–48.
33. Nah SS, Choi IY, Yoo B, Kim YG, Moon HB, Lee CK. Advanced glycation end products increases matrix metalloproteinase-1,-3, and-13, and TNF-α in human osteoarthritic chondrocytes. FEBS Lett 2007;581:1928–32.
34. Nah SS, Choi IY, Lee CK, Oh JS, Kim YG, Moon HB, et al. Effects of advanced glycation end products on the expression of COX-2, PGE2 and NO in human osteoarthritic chondrocytes. Rheumatology (Oxford) 2008;47:425–31.
35. Eyre DR, Weis MA, Wu JJ. Articular cartilage collagen: an irreplaceable framework. Eur Cell Mater 2006;12:57–63.
36. Verzijl N, DeGroot J, Zaken CB, Braun-Benjamin O, Maroudas A, Bank RA, et al. Crosslinking by advanced glycation end products increases the stiffness of the collagen network in human articular cartilage: a possible mechanism through which age is a risk factor for osteoarthritis. Arthritis Rheum 2002;46:114–23.
37. Chen YJ, Sheu ML, Tsai KS, Yang RS, Liu SH. Advanced glycation end products induce peroxisome proliferator-activated receptor γ down-regulation-related inflammatory signals in human chondrocytes via Toll-like receptor-4 and receptor for advanced glycation end products. PLoS One 2013;8:e66611.
38. Steenvoorden MM, Huizinga TW, Verzijl N, Bank RA, Ronday HK, Luning HA, et al. Activation of receptor products in osteoarthritis leads to increased stimulation of chondrocytes and synoviocytes. Arthritis Rheum 2006;54:253–63.
39. Rosa SC, Gonçalves J, Judas F, Mobasheri A, Lopes C, Mendes AF. Impaired glucose transporter-1 degradation and increased glucose transport and oxidative stress in response to high glucose in chondrocytes from osteoarthritic versus normal human cartilage. Arthritis Res Ther 2009;11:R80.
40. Stürmer T, Brenner H, Brenner RE, Günther KP. Non-insulin dependent diabetes mellitus (NIDDM) and patterns of osteoarthritis: the Ulm osteoarthritis study. Scand J Rheumatol 2001;30:169–71.
41. Felmeden DC, Spencer CG, Belgore FM, Blann AD, Beevers DG, Lip GY. Endothelial damage and angiogenesis in hypertensive patients: relationship to cardiovascular risk factors and risk factor management. Am J Hypertens 2003;16:11–20.
42. Kiefer FN, Neysari S, Humar R, Li W, Munk VC, Battegay EJ. Hypertension and angiogenesis. Curr Pharm Desgn 2003;9:1733–44.
43. Karter Y, Aydın S, Curgunlu A, Uzun H, Ertürk N, Vehid S, et al. Endothelium and angiogenesis in white coat hypertension. J Hum Hypertens 2004;18:809–14.
44. Otero M, Reino JJ, Gualillo O. Synergistic induction of nitric oxide synthase type II: in vitro effect of leptin and interferon-γ in human chondrocytes and ATDC5 chondrogenic cells. Arthritis Rheum 2003;48:404–9.
45. Iliopoulos D, Malizos KN, Tsezou A. Epigenetic regulation of leptin affects MMP-13 expression in osteoarthritic chondrocytes: possible molecular target for osteoarthritis therapeutic intervention. Ann Rheum Dis 2007;66:1616–21.
46. Sanna V, Di Giacomo A, La Cava A, Lechler RI, Fontana S, Zappacosta S, et al. Leptin surge precedes onset of autoimmune encephalomyelitis and correlates with development of pathogenic T cell responses. J Clin Invest 2003;111:241–50.
47. Faggioni R, Feingold KR, Grunfeld C. Leptin regulation of the immune response and the immunodeficiency of malnutrition. FASEB J 2001;15:2565–71.
48. Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol 2005;174:5789–95.
49. Šenolt L, Housa D, Vernerova Z, Jirasek T, Svobodová R, Veigl D, et al. Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. Ann Rheum Dis 2007;66:458–63.
50. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84:351–8.
51. Miró J, Paredes S, Rull M, Queral R, Miralles R, Nieto R, et al. Pain in older adults: a prevalence study in the Mediterranean region of Catalonia. Eur J Pain 2007;11:83–92.
52. Donald IP, Foy C. A longitudinal study of joint pain in older people. Rheumatology (Oxford) 2004;43:1256–60.
53. Thomas E, Peat G, Harris L, Wilkie R, Croft PR. The prevalence of pain and pain interference in a general population of older adults: cross-sectional findings from the North Staffordshire Osteoarthritis Project (NorStOP). Pain 2004;110:361–8.
54. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med 2003;139 Part 1:330–6.
55. McCrae F, Shouls J, Dieppe P, Watt I. Scintigraphic assessment of osteoarthritis of the knee joint. Ann Rheum Dis 1992;51:938–42.
56. Creamer P, Hunt M, Dieppe P. Pain mechanisms in osteoarthritis of the knee: effect of intraarticular anesthetic. J Rheumatol 1996;23:1031–6.
57. Richey PA, Johnson KC, Neiberg RH, Bahnson JL, Singhal K, Coday M, et al. Association of the intensive lifestyle intervention with total knee replacement in the Look AHEAD (Action for Health in Diabetes) clinical trial. J Arthroplasty 2020;35:1576–82.
58. Foy CG, Lewis CE, Hairston KG, Miller GD, Lang W, Jakicic JM, et al. Intensive lifestyle intervention improves physical function among obese adults with knee pain: findings from the Look AHEAD trial. Obesity 2011;19:83–93.
59. Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD study. Obesity 2014;22:5–13.
60. Verzijl N, Bank RA, TeKoppele JM, DeGroot J. AGEing and osteoarthritis: a different perspective. Curr Opin Rheumatol 2003;15:616–22.
61. Ding C, Cicuttini F, Scott F, Cooley H, Jones G. Association between age and knee structural change: a cross sectional MRI based study. Ann Rheum Dis 2005;64:549–55.
62. Lacey RJ, Thomas E, Duncan RC, Peat G. Gender difference in symptomatic radiographic knee osteoarthritis in the Knee Clinical Assessment–CAS (K): a prospective study in the general population. BMC Musculoskelet Disord 2008;9:82.
63. Amin S, Niu J, Guermazi A, Grigoryan M, Hunter DJ, Clancy M, et al. Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. Ann Rheum Dis 2007;66:18–22.
64. Andersson H, Ejlertsson G, Leden I. Widespread musculoskeletal chronic pain associated with smoking: an epidemiological study in a general rural population. Scand J Rehabil Med 1998;30:185–91.
65. Sandmark H, Hogstedt C, Lewold S, Vingård E. Osteoarthrosis of the knee in men and women in association with overweight, smoking, and hormone therapy. Ann Rheum Dis 1999;58:151–5.
66. Davis MA, Ettinger WH, Neuhaus JM, Cho SA, Hauck WW. The association of knee injury and obesity with unilateral and bilateral osteoarthritis of the knee. Am J Epidemiol 1989;130:278–88.

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BRIEF REPORT

Foot Osteoarthritis Frequency and Associated Factors in a Community-Based Cross-Sectional Study of White and African American Adults

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Objective. Few studies have explored foot osteoarthritis (OA) in the general population. The purpose of this study was to determine the frequency of foot OA and identify associated factors in a cross-sectional analysis of a large community-based cohort.

Methods. Data were from the 2013–2015 study visit of the Johnston County OA Project. Radiographic OA of the foot was defined using the La Trobe radiographic atlas (≥2 osteophytes or joint space narrowing in at least 1 of 5 joints). Symptomatic OA of the foot was defined as foot radiographic OA with pain, aching, or stiffness in the same foot. At the foot-level, separate logistic regression models with generalized estimating equations to account for intraperson correlations were performed to examine associations of foot radiographic OA or symptomatic OA with age, body mass index (BMI), sex, race, educational attainment, and previous foot injury.

Results. Of 864 participants with available data (mean age 71 years, mean BMI 30 kg/m^2, 68% women, 33% African American, 13% <12 years of schooling), 22% had foot radiographic OA, 20% had foot symptoms, and 5% had foot symptomatic OA. Radiographic, but not symptomatic, foot OA was more common in African American than White participants. Participants with obesity, compared to normal weight, had >2 times the odds of radiographic OA and >5 times the odds of symptomatic OA in adjusted models.

Conclusion. Foot radiographic OA and foot symptoms were common in the sample, but both conditions simultaneously (i.e., symptomatic OA) occurred infrequently. Notably, obesity was linked with foot symptomatic OA, perhaps implicating metabolic or mechanical influences.

INTRODUCTION

Osteoarthritis (OA) is a painful disease and a leading cause of disability (1) that affects an estimated 90 million adults in the US (2). Although studies have evaluated lower extremity OA at the knee and hip, few have focused on foot radiographic OA. First metatarsophalangeal joint radiographic OA, a common joint site for OA in the foot, ranges from a prevalence of 6.3% in rural African women ≥40 years of age (3) to 42% in adults 62–94 years of age residing in a retirement village in Australia (4). Even less is known regarding the prevalence of foot radiographic OA with symptoms (foot symptomatic OA). Only 1 cohort study of community-dwelling adults ≥50 years of age has examined prevalence of foot symptomatic OA: the Clinical Assessment Study of the Foot (CASF) of 5,109 adults registered with 4 general practices in North Staffordshire, UK. In the CASF, only participants reporting foot pain during the last 12 months completed foot radiography (560 participants), and the estimated frequency of symptomatic OA overall was 16.7%, with 7.8% having symptomatic OA of the first metatarsophalangeal joint (5). Older age, female

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- This is the first large community-based study to examine the frequency of foot osteoarthritis (OA) in a sample that includes African American and White older adults.
- Both radiographic OA and symptoms of the foot are common in older adults.
- Radiographic foot OA may be more common in African American than White adults, but there were no differences in symptomatic foot OA by race.
- Obesity is associated with radiographic and symptomatic foot OA. Given the frequency of foot radiographic OA, foot symptoms, and higher body mass index in older individuals, further work on patterns and interrelations of these elements is warranted.

sex, obesity, socioeconomic status, and history of joint injury are commonly associated with OA at the knee and hip, and results from the CASF suggest that these factors may also be related to foot symptomatic OA (5,6). No studies have considered whether radiographic and symptomatic foot OA differ by race.

To enhance our understanding of foot OA in populations, we used data from a large community-based biracial cohort in which participants completed radiography of the foot, regardless of presence of foot pain, to determine the frequency of foot radiographic OA and symptomatic OA and the factors potentially associated with foot OA.

SUBJECTS AND METHODS

Study participants. Participants were from the Johnston County OA Project (JoCo OA), a community-based cohort study of individuals with and without OA (7). Noninstitutionalized White and African American residents age ≥45 years were recruited from 6 communities within Johnston County, North Carolina. Because the parent study was designed to examine racial differences in OA development and progression longitudinally, African American participants were oversampled to allow for such comparisons (approximately one-third of the sample). For the present study, data were obtained from individuals who attended the 2013–2015 study visit of the JoCo OA. At this study visit, all participants were at least 55 years of age. This study was approved by the Institutional Review Boards of the University of North Carolina School at Chapel Hill and the Centers for Disease Control and Prevention. All participants provided written informed consent prior to data collection.

Foot osteoarthritis and symptoms. Standardized weight-bearing anteroposterior and lateral radiographic images of the foot were obtained. Based on the La Trobe radiographic atlas (4,8), osteophytes and joint space narrowing were graded by an expert musculoskeletal radiologist (JBR) for the first metatarsophalangeal joint, first and second cuneometatarsal joints, navicular–first cuneiform joint, and talonavicular joint. Foot radiographic OA was defined as a score of ≥2 for osteophytes or joint space narrowing in at least 1 of the 5 joint sites. Presence of general foot symptoms was assessed by an affirmative response to the question: "On most days of any one month in the last 12 months did you have pain, aching or stiffness in your [left/right] foot?" Symptomatic OA was defined as foot radiographic OA and general foot symptoms in the same foot.

Demographic and clinical characteristics. Because race, age, sex, body mass index (BMI), history of injury, and socioeconomic status (e.g., education) are key factors associated with OA (9), these variables were selected as covariates in analyses. Race, age, sex, and educational attainment were collected via self-report, with race (African American/White), sex (men/women), and education (<12 versus ≥12 years of schooling) defined as dichotomous variables. For these analyses, age was a continuous variable. Height was measured using a calibrated stadiometer, and weight was measured using a balance-beam scale. Both measures were taken without shoes. BMI was calculated as weight in kg/height in meters^2. BMI was categorized as obese (≥30 kg/m^2), overweight (25 to <30 kg/m^2), and normal weight (<25 kg/m^2) for analyses. History of foot injury was obtained via questionnaire consisting of 2 questions: "Has a doctor ever told you that you broke or fractured your [right/left] foot?" and "Other than a fracture, have you injured your [right/left] foot enough to require a cane, cast, or crutch for 2 weeks or longer?" History of foot injury was defined as an affirmative response to at least 1 of these questions and was determined separately for each foot.

Statistical analysis. Means and SDs for continuous variables, and frequencies and percentages for categorical variables, were calculated for demographic and clinical characteristics. At the level of the foot (rather than the participant), separate logistic regression models with generalized estimating equations (GEEs; to account for intraperson correlations of the 2 foot [right/left] observations per participant) were performed to examine discrete associations (odds ratios [ORs]) of foot radiographic OA or symptomatic OA with age, BMI, sex, race, education, and history of foot injury. The presence or absence of foot injury was linked to the same side [right/left] as the foot examined in analyses. Next, multiple logistic regression models with GEEs were performed for foot radiographic OA or symptomatic OA outcomes adjusting for the above factors. All statistical analyses were completed using SAS system software, version 9.4.

RESULTS

Study participants. Data were obtained from 908 individuals who attended the 2013–2015 study visit of the JoCo OA. Foot radiographs were not available for 44 participants. These participants without foot radiographs were slightly older with higher BMIs

and were more likely to be men, African American, and have foot pain. Of the 864 participants with available data, the mean ± SD age was 71 ± 8 years, and the mean BMI was 31 ± 6 kg/m^2. More than two-thirds of participants were women (68%), 33% were African American, 13% had <12 years of education, 22% had foot radiographic OA, 20% had foot symptoms, 5% had symptomatic OA, and 4% reported prior foot injury. Among those with foot radiographic OA, 27% had foot symptoms compared to 19% without foot radiographic OA. The 864 participants contributed 1,728 feet for foot-specific analyses. One individual was missing data on foot symptoms, and thus, 863 participants had available data for the foot symptomatic OA analyses. Two participants were missing foot injury data, and 3 were missing data on education.

Factors associated with foot OA. After adjusting for age, sex, race, education, and injury, compared to those without obesity, individuals with obesity (BMI ≥30 kg/m^2) had 2.3 times the odds of having foot radiographic OA (Table 1). Additionally, older age was associated with foot radiographic OA (Table 1) after adjusting for BMI, sex, race, education, and injury. In unadjusted analyses, African Americans had 46% higher odds of having foot radiographic OA compared to White participants (OR 1.46 [95% confidence interval (95% CI) 1.06–2.03]); this association was slightly attenuated after adjustment for covariates (adjusted OR [OR_{adj}] 1.39 [95% CI 0.99–1.97]) (Table 1).

Despite small numbers for foot symptomatic OA contributing to imprecise estimates (n = 46), similar to the analyses of foot radiographic OA, after adjusting for age, sex, race, education, and injury, individuals with obesity had >5 times the odds of having foot symptomatic OA compared to participants who were normal weight (OR_{adj} 5.13 [95% CI 1.49–17.7]) (Table 2). The odds of foot symptomatic OA by race were not statistically different in either unadjusted or adjusted models. Education of <12 years was associated with foot symptomatic OA in unadjusted models (OR_{adj} 2.15 [95% CI 1.04–4.45]); this association was attenuated after adjustment (OR_{adj} 1.92 [95% CI 0.86–4.35]) (Table 2). The odds of foot symptomatic OA were much higher among those with foot injury than without foot injury, although results were not statistically significant (OR_{adj} 3.18 [95% CI 0.76–13.3]).

DISCUSSION

To our knowledge, this is the first biracial community-based study of middle-to-older aged adults to examine the frequency of foot OA. Results of this study suggest that obesity may be linked to foot OA, and that foot radiographic OA may be more common among African American than White adults.

In this study, foot radiographic OA was common in older adults, with 1 of 5 older adults having foot radiographic OA, which fits within the range of frequencies of foot radiographic OA in older adults (5–43%) reported in previous studies (3,10,11). Foot symptomatic OA was less frequent, affecting 1 of 20 individuals. These results suggest a lower frequency than previously stated in the literature, with the CASF reporting 12% symptomatic OA at the midfoot (6), 7.8% symptomatic OA at the first metatarsophalangeal joint (5), and 16.7% overall (5). The current study and the CASF used different source populations, recruitment approaches, and definitions of foot symptomatic OA, which may have contributed to the differences in the estimates of symptomatic OA occurrence.

Presence of foot symptoms in the current study (20%) corresponds to previous reports. In a population-based survey in The Netherlands, 20% of individuals age ≥65 years reported nontraumatic foot symptoms, the majority of which involved pain (12). A population-based study from Australia reported that 17% of all adults had foot pain (13), and the Framingham Foot Study reported 22% had foot pain on most days (14). The frequency of foot symptoms in this study represents a public health concern,

Table 1. Unadjusted and adjusted associations of Johnston County Osteoarthritis Project participant characteristics with foot radiographic osteoarthritis (rOA)*

Characteristic	Overall (n = 864)	Foot rOA (n = 191, 22.1%)	No Foot rOA (n = 673, 77.9%)	OR (95% CI)†	Adjusted OR (95% CI)‡
Age, mean ± SD years	71.2 ± 7.6	72.1 ± 7.9	70.9 ± 7.4	1.02 (0.99–1.04)	1.03 (1.01–1.06)
BMI ≥30 kg/m^2	435/864 (50.3)	118/191 (61.8)	317/673 (47.1)	2.18 (1.31–3.65)	2.27 (1.34–3.86)
BMI 25 to <30 kg/m^2	296/864 (34.3)	52/191 (27.2)	244/673 (36.3)	1.28 (0.73–2.24)	1.39 (0.78–2.46)
BMI <25 kg/m^2	133/864 (15.4)	21/191 (11.0)	112/673 (16.6)	Ref.	Ref.
Women	589/864 (68.2)	134/191 (70.2)	455/673 (67.6)	1.21 (0.86–1.70)	1.14 (0.80–1.62)
Men	275/864 (31.8)	57/191 (29.8)	218/673 (32.4)	Ref.	Ref.
African American	289/864 (33.4)	78/191 (40.8)	211/673 (31.4)	1.46 (1.06–2.03)	1.39 (0.99–1.97)
White	575/864 (66.6)	113/191 (59.2)	462/673 (68.6)	Ref.	Ref.
<12 years education	114/861 (13.2)	31/191 (16.2)	83/670 (12.4)	1.27 (0.83–1.95)	1.06 (0.68–1.66)
12+ years education	747/861 (86.8)	160/191 (83.8)	587/670 (87.6)	Ref.	Ref.
Foot injury	33/862 (3.8)	9/190 (4.7)	24/672 (3.6)	1.34 (0.53–3.40)	1.55 (0.59–4.06)
No foot injury	829/862 (96.2)	181/190 (95.3)	648/672 (96.4)	Ref.	Ref.

* Values are the no./total no. (%) unless indicated otherwise. 95% CI = 95% confidence interval; BMI = body mass index; OR = odds ratio; Ref. = referent.
† Adjusted only for intraperson correlation using generalized estimating equations.
‡ Adjusted for intraperson correlation and all other listed covariates.

Table 2. Unadjusted and adjusted associations of Johnston County Osteoarthritis Project participant characteristics with foot symptomatic osteoarthritis (SxOA)*

Characteristic	Overall (n = 863)	Foot SxOA (n = 46, 5.3%)	No Foot SxOA (n = 817, 94.7%)	OR (95% CI)†	Adjusted OR (95% CI)‡
Age, mean ± SD years	71.2 ± 7.6	71.0 ± 7.1	71.2 ± 7.6	1.01 (0.97–1.05)	1.02 (0.97–1.07)
Obese	435/863 (50.4)	34/46 (73.9)	401/817 (49.1)	4.60 (1.40–15.1)	5.13 (1.49–17.7)
Overweight	296/863 (34.3)	9/46 (19.6)	287/817 (35.1)	1.64 (0.44–6.18)	1. 81 (0.44–7.53)
Normal weight	132/863 (15.3)	3/46 (6.5)	129/817 (15.8)	Ref.	Ref.
Women	588/863 (68.1)	35/46 (76.1)	553/817 (67.7)	1.49 (0.72–3.06)	1.47 (0.66–3.30)
Men	275/863 (31.9)	11/46 (23.9)	264/817 (32.3)	Ref.	Ref.
African American	289/863 (33.5)	15/46 (32.6)	274/817 (33.5)	0.97 (0.50–1.88)	0. 76 (0.37–1.68)
White	574/863 (66.5)	31/46 (67.4)	543/817 (66.5)	Ref.	Ref.
<12 years education	114/860 (13.3)	11/46 (23.9)	103/814 (12.7)	2.15 (1.04–4.45)	1.93 (0.86–4.35)
12+ years education	746/860 (86.7)	35/46 (76.1)	711/814 (87.3)	Ref.	Ref.
Foot injury	33/861 (3.8)	4/46 (8.7)	29/815 (3.6)	2.82 (0.72–11.1)	3.18 (0.76–13.3)
No foot injury	828/861 (96.2)	42/46 (91.3)	786/815 (96.4)	Ref.	Ref.

* Values are the no./total no. (%) unless indicated otherwise. 95% CI = 95% confidence interval; OR = odds ratio; Ref. = referent.
† Adjusted only for intraperson correlation using generalized estimating equations.
‡ Adjusted for intraperson correlation and all other listed covariates.

not dissimilar to knee pain (regardless of knee OA status), as anatomic pain often indicates an underlying musculoskeletal condition that interferes with daily activities. Thus, further work is necessary to evaluate the impact of foot symptoms upon mobility and other physical functioning in the community. Even after adjusting for age, obesity, smoking, and symptoms of depression, the Framingham Foot Study found that men with foot pain had twice the odds of having limited mobility (OR_{adj} 2.0 [95% CI 1.14–3.50]) and women with foot pain had nearly 60% greater odds of having mobility limitations (OR_{adj} 1.59 [95% CI 1.03–2.46]) (14).

The current study shows that obesity, similar to the knee (9) and ankle (15), was linked to OA at the foot, and our results are consistent with findings from the CASF that demonstrated an association between symptomatic OA of the midfoot and obesity (6). The present analysis does not suggest the direction of the obesity–foot OA association, but longitudinal analyses could advance the understanding of obesity as a mechanical or metabolic factor for foot OA and pain, which ultimately could guide interventions.

Although several studies have reported foot OA frequency, to our knowledge, this is the first study to examine frequency of foot OA in a cohort including African Americans, allowing for comparisons of foot OA by race. Notably, African Americans had 40% higher odds of foot radiographic OA than White participants, even after adjusting for covariates. The lack of racial differences for foot symptomatic OA in our study may be due to the small numbers of individuals with foot symptomatic OA and remains of interest for future studies as symptomatic OA is considered to be a more clinically relevant outcome than radiographic OA.

In adjusted models, older age was associated with foot radiographic OA. Estimates for foot radiographic OA and symptomatic OA were higher, but not statistically significant, for women versus men and those with foot injury versus without injury. Education was not associated with foot radiographic OA, but estimates for foot symptomatic OA were higher for those with <12 years versus ≥12 years of schooling. Overall, these results were consistent with prior literature in that foot OA, as seen with knee and hip OA, is more common with older age, female sex, lower educational attainment, and injury history (5,6,9). The anatomic and biomechanical complexity of the foot, with 26 bones and 33 joints, may lead to differences in factors associated with foot OA compared to those observed for large, weight-bearing joints like the knee or hip.

There are several limitations to this study. Because of the cross-sectional design, the direction of associations cannot be determined. Therefore, it is unknown if obesity resulted in foot OA or if foot OA led to obesity. Longitudinal analyses of the relationship between OA risk factors and foot OA may help in examining directionality of associations, how those associations may change with age, and how demographic and clinical factors relate to progression of foot OA. Additionally, this sample consisted primarily of older adults, so results may not be generalizable to younger adults. Also, JoCo OA participants who were not able to return for the 2013–2015 clinic visit were generally older and in poorer health than those who attended, and thus our sample may not fully represent an older adult population. For these analyses, we defined foot symptoms using a question that did not specify a location within the foot. This approach for defining symptoms was suitable for our purpose of examining foot symptomatic OA in general, but future investigations of symptomatic OA at specific joints of the foot, such as the 5 joint sites included in the La Trobe atlas, will require matching the region of symptoms to the specific location of joint pathology. The assessment of foot OA based only on radiographic features of osteophytes and joint space narrowing is a further limitation because it does not capture the multiple tissues involved in OA that may be observed with other imaging techniques.

In conclusion, foot radiographic OA and the presence of pain, aching, or stiffness in the foot were common, occurring in 1 of 5

older adults. However, foot symptomatic OA was less frequent in this community-based biracial cohort than reported by other studies. In addition, obesity increased the odds for foot OA, suggesting that weight may be an important component of strategies for managing foot OA, especially for individuals with symptomatic OA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Golightly had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Flowers, Nelson, Hannan, Hillstrom, Renner, Jordan, Golightly.

Acquisition of data. Renner, Jordan.

Analysis and interpretation of data. Flowers, Nelson, Hannan, Hillstrom, Renner, Jordan, Golightly.

REFERENCES

1. Theis KA, Roblin DW, Helmick CG, Luo R. Prevalence and causes of work disability among working-age U.S. adults, 2011–2013, NHIS. Disabil Health J 2018;11:108–15.
2. Jafarzadeh SR, Felson DT. Updated estimates suggest a much higher prevalence of arthritis in United States adults than previous ones. Arthritis Rheumatol 2018;70:185–92.
3. Brighton SW, De La Harpe AL, Van Staden DA. The prevalence of osteoarthrosis in a rural African community. Br J Rheumatol 1985;24: 321–5.
4. Menz HB, Munteanu SE, Landorf KB, Zammit GV, Cicuttini FM. Radiographic evaluation of foot osteoarthritis: sensitivity of radiographic variables and relationship to symptoms. Osteoarthritis Cartilage 2009; 17:298–303.
5. Roddy E, Thomas MJ, Marshall M, Rathod T, Myers H, Menz HB, et al. The population prevalence of symptomatic radiographic foot osteoarthritis in community-dwelling older adults: cross-sectional findings from the clinical assessment study of the foot. Ann Rheum Dis 2015;74:156–63.
6. Thomas MJ, Peat G, Rathod T, Marshall M, Moore A, Menz HB, et al. The epidemiology of symptomatic midfoot osteoarthritis in community-dwelling older adults: cross-sectional findings from the Clinical Assessment Study of the Foot. Arthritis Res Ther 2015;17: 178.
7. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 2007;34:172–80.
8. Menz HB, Munteanu SE, Landorf KB, Zammit GV, Cicuttini FM. Radiographic classification of osteoarthritis in commonly affected joints of the foot. Osteoarthritis Cartilage 2007;15:1333–8.
9. Vina ER, Kwoh CK. Epidemiology of osteoarthritis. Curr Opin Rheumatol 2018;30:160–7.
10. Wilder FV, Barrett JP, Farina EJ. The association of radiographic foot osteoarthritis and radiographic osteoarthritis at other sites. Osteoarthritis Cartilage 2005;13:211–5.
11. Van Saase JL, Van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989;48:271–80.
12. Gorter KJ, Kuyvenhoven MM, de Melker RA. Nontraumatic foot complaints in older people: a population-based survey of risk factors, mobility, and well-being. J Am Podiatr Med Assoc 2000;90:397–402.
13. Hill CL, Gill TK, Menz HB, Taylor AW. Prevalence and correlates of foot pain in a population-based study: the North West Adelaide health study. J Foot Ankle Res 2008;1:2.
14. Menz HB, Dufour AB, Casey VA, Riskowski JL, McLean RR, Katz P, et al. Foot pain and mobility limitations in older adults: the Framingham Foot Study. J Gerontol A Biol Sci Med Sci 2013;68:1281–5.
15. Lateef S, Golightly YM, Renner JB, Jordan JM, Nelson AE. A cross-sectional analysis of radiographic ankle osteoarthritis frequency and associated factors: the Johnston County Osteoarthritis Project. J Rheumatol 2017;44:499–504.

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Cancer Risk in a Large Inception Systemic Lupus Erythematosus Cohort: Effects of Demographic Characteristics, Smoking, and Medications

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Objective. To assess cancer risk factors in incident systemic lupus erythematosus (SLE).

Methods. Clinical variables and cancer outcomes were assessed annually among incident SLE patients. Multivariate hazard regression models (overall risk and most common cancers) included demographic characteristics and time-dependent medications (corticosteroids, antimalarial drugs, immunosuppressants), smoking, and the adjusted mean Systemic Lupus Erythematosus Disease Activity Index 2000 score.

Results. Among 1,668 patients (average 9 years follow-up), 65 cancers occurred: 15 breast, 10 nonmelanoma skin, 7 lung, 6 hematologic, 6 prostate, 5 melanoma, 3 cervical, 3 renal, 2 each gastric, head and neck, and thyroid, and 1 each rectal, sarcoma, thymoma, and uterine cancers. Half of the cancers (including all lung cancers) occurred in past/current smokers, versus one-third of patients without cancer. Multivariate analyses indicated that overall cancer risk was related primarily to male sex and older age at SLE diagnosis. In addition, smoking was associated with lung cancer. For breast cancer risk, age was positively associated and antimalarial drugs were negatively associated. Antimalarial drugs and higher disease activity were also negatively associated with nonmelanoma skin cancer risk, whereas age and cyclophosphamide were positively associated. Disease activity was associated positively with hematologic and negatively with nonmelanoma skin cancer risk.

Conclusion. Smoking is a key modifiable risk factor, especially for lung cancer, in SLE. Immunosuppressive medications were not clearly associated with higher risk except for cyclophosphamide and nonmelanoma skin cancer. Antimalarials were negatively associated with breast cancer and nonmelanoma skin cancer risk. SLE activity was associated positively with hematologic cancer and negatively with nonmelanoma skin cancer. Since the absolute number of cancers was small, additional follow-up will help consolidate these findings.

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SIGNIFICANCE & INNOVATIONS

- Age at systemic lupus erythematosus (SLE) diagnosis was associated with higher breast cancer risk, while antimalarial drugs were associated with lower risk.
- Antimalarial drugs were also associated with lower nonmelanoma skin cancer risk, whereas age and cyclophosphamide were positively associated with nonmelanoma skin cancer risk.
- Disease activity was associated positively with hematologic and negatively with nonmelanoma skin cancer risk.
- These findings not only help us better understand cancer risk in SLE, but also suggest potential approaches to improve the cancer risk profile in SLE and provide future directions for research.

INTRODUCTION

There has been increasing interest in cancer risk and systemic autoimmune rheumatic diseases, including systemic lupus erythematosus (SLE) (1). On one hand, inflammation may promote cancer occurrence (2), while on the other, some of the medications used in SLE and other autoimmune diseases could be associated with cancer risk (e.g., cyclophosphamide, which is an alkylating agent) (3). Previous studies of cancer risk in SLE were often limited by sample size or reliance on administrative data sources instead of clinical data (4). No studies to date have focused on incident SLE patients. This absence may have lead to incomplete data on immunosuppressive drug exposures and other clinical variables. To overcome these limitations, we studied cancer occurrence in a very large multicenter cohort of clinically confirmed incident SLE patients (5), at centers in North America, Europe, and Asia, with specific attention to clinical features, medications, and the onset of comorbidity, including cancer.

PATIENTS AND METHODS

Patients meeting American College of Rheumatology (ACR) classification criteria (6) for new-onset SLE (within 15 months of diagnosis) were enrolled into the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort, across 33 centers (from 1999 to 2011). From the first visit (time zero), patients were followed at yearly intervals according to a standardized protocol, with information on disease activity, medications, and new cancer diagnoses (recorded by the study physician and confirmed by reviewing medical files, including pathology reports, where available).

Multivariate proportional hazards regression was performed, using baseline demographic characteristics (age at SLE diagnosis, sex, race/ethnicity) and time-dependent variables for drugs (corticosteroids, antimalarial drugs, immunosuppressive drugs), smoking, and Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) scores (recorded yearly, then averaged over time using the "adjusted mean SLEDAI" approach, where the result has the same units as the original SLEDAI-2K) (7). The values for adjusted mean SLEDAI-2K scores over time were divided into quartiles for the risk set related to each event that occurred within the cohort (between first visit to end of the study; thus the time axis was time since cohort entry). Our primary time-dependent variable for disease activity was then categorized as ever having scored in the highest quartile of SLE activity, up to the time of each risk set (cancer event). Sensitivity analyses also assessed cancer risk according to whether or not subjects had been in a persistently low disease state (lowest quartile of disease activity as defined above), for each risk set.

We performed univariate and multivariate models; the primary multivariate models adjusted for baseline demographic

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characteristics (age at SLE diagnosis, sex, race/ethnicity), a time-dependent variable for ever smoking, a time-dependent variable indicating whether the patient had ever had a mean adjusted SLEDAI-2K value in the highest disease activity quartile, and time-varying SLE medication exposures (ever/never use of corticosteroids, antimalarial drugs, immunosuppressive agents). The variable for race/ethnicity was dichotomous (White versus all other categories). Given the relatively low number of outcome events, we also ran more parsimonious multivariable models for each exposure of interest, adjusting only for demographics (age, sex, race/ethnicity), but these results are not shown because they were not significantly changed from the full model results.

As well as evaluating potential risk factors for overall cancer risk, we also considered the most common cancer types individually. In some of those analyses, we had zero events in certain ever/never exposure categories, which required altering the exposure definition to allow evaluation of the covariate. For example, if all cases of a certain cancer type had ever been antimalarial exposed, we instead used antimalarial use as cumulative exposure for 5 years or more in our model. For some malignancy types, there were no exposures to certain drugs (e.g., biologics), so in such a case, that covariate could not be included in that specific regression model. Analyses were performed using R software, with verification of underlying proportional hazards assumptions using Schoenfeld residuals. This study was approved by local ethics boards, and patients provided signed informed consent to participate in the cohort study.

RESULTS

Of 1,848 newly diagnosed SLE patients enrolled, 1,668 had at least 1 follow-up visit and formed the cohort analyzed in this study. These patients were followed until death, last visit, or the end of the study interval for this analysis (March 2019). Table 1 shows the baseline characteristics of the individuals, divided into those who ultimately had a cancer or remained cancer free.

Table 1. Descriptive analyses for baseline characteristics of SLE patients, specifically for those who ultimately developed cancer versus those who remained cancer free*

Categories	No cancer (n = 1,603)	Cancer (n = 65)
Female	1,432 (89.3)	48 (73.8)
White race/ethnicity	780 (48.7)	44 (67.7)
Age at SLE diagnosis, mean ± SD years	34.2 ± 13.1	45.6 ± 14.5
Mean SLE duration, mean ± SD months	5.60 ± 4.20	5.50 ± 3.7
Top quartile SLEDAI-2K	539 (33.6)	16 (24.6)
Current or past smoker	534 (33.3)	31 (47.7)
Steroids ever	1,201 (74.9)	45 (69.2)
Cyclophosphamide ever	139 (8.7)	3 (4.6)
Azathioprine ever	457 (28.5)	16 (24.6)
Methotrexate ever	187 (11.7)	9 (13.8)
Mycophenolate ever	244 (15.2)	7 (10.8)
Antimalarial ever	1,263 (78.8)	50 (76.9)
Biologic ever	39 (2.4)	0 (0.0)

* Values are the number (%) unless indicated otherwise. SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

Table 2. Hazard ratios (HRs) for overall cancer risk in SLE*

All types of cancer, 65 events	Unadjusted HR (95% CI)	Adjusted HR (95% CI)†
Age at SLE diagnosis, years	1.06 (1.04–1.07)‡	1.05 (1.03–1.06)‡
Female	0.35 (0.20–0.60)‡	0.47 (0.26–0.85)‡
White race/ethnicity	2.24 (1.33–3.78)‡	1.34 (0.76–2.37)
Top quartile SLE activity ever	0.59 (0.35–1.02)	0.84 (0.47–1.52)
Smoking ever	1.72 (1.06–2.80)‡	1.21 (0.73–2.01)
Steroids ever	0.61 (0.35–1.07)	0.78 (0.42–1.47)
Cyclophosphamide ever	0.72 (0.33–1.58)	1.10 (0.46–2.61)
Azathioprine ever	0.68 (0.40–1.15)	0.92 (0.52–1.65)
Methotrexate ever	1.39 (0.78–2.49)	1.63 (0.89–2.99)
Mycophenolate ever	0.81 (0.45–1.45)	1.18 (0.62–2.26)
Antimalarial ever	0.64 (0.34–1.20)	0.64 (0.33–1.24)
Biologic ever	0.62 (0.23–1.73)	0.70 (0.24–2.05)

* 95% CI = 95% confidence interval; SLE = systemic lupus erythematosus.
† Adjusted for all variables shown; disease activity, smoking, and all drug variables were time dependent.
‡ Statistically significant.

Over a follow-up of 15,014 person-years (mean and median 9), 65 cancers occurred (4.3 events per 1,000 patient-years). These included 15 breast cancers, 10 nonmelanoma skin, 7 lung, 6 hematologic, 6 prostate, 5 melanoma, 3 cervical, 3 renal, 2 gastric, 2 head and neck, 2 thyroid, and 1 each rectal, sarcoma, thymoma, and uterine cancer. No patient had >1 type of cancer. The hematologic cancers included 3 non-Hodgkin's lymphoma, 1 acute myeloid leukemia, 1 chronic myeloid leukemia, and 1 myeloma.

Almost half of cancer cases (including all of the lung cancers) occurred in past/current smokers, while only one-third of patients without cancer smoked prior to the onset of the event. As suggested in Table 1 and further verified by the univariate hazard ratios (HRs) in Table 2, older age at SLE diagnosis, male sex, White race/ethnicity, and smoking were associated with greater cancer risk overall. However, the multivariate regressions indicated that among SLE patients, overall cancer risk was related primarily to older age at SLE diagnosis and male sex. There was no evidence of violation of the proportional hazards assumption in any of our models.

In the multivariate analyses specifically for breast cancer (Table 2), older age at SLE diagnosis remained a risk factor, while antimalarial use was associated with a lower risk of breast cancer. This effect of antimalarial drugs was also seen for nonmelanoma skin cancer (Table 2), where both age at SLE diagnosis and cyclophosphamide use were also strongly associated with risk. Interestingly, patients who scored at least once in the highest quartile of SLE disease activity were at lower risk for nonmelanoma skin cancer.

Table 3. Hazard ratios (HRs) for breast, nonmelanoma skin, lung, and hematologic cancers*

Cancer type and risk	Unadjusted HR (95% CI)	Adjusted HR (95% CI)†
Breast cancer, 15 events		
Age at SLE diagnosis, years	1.06 (1.03–1.10)‡	1.06 (1.02–1.10)‡
White race/ethnicity	0.93 (0.34–2.56)	0.49 (0.16–1.55)
Top quartile SLE activity ever	0.53 (0.17–1.66)	0.73 (0.20–2.70)
Smoking ever	0.98 (0.34–2.87)	0.88 (0.29–2.65)
Steroids ever	0.45 (0.15–1.31)	0.48 (0.13–1.75)
Cyclophosphamide ever	1.08 (0.24–4.78)	2.51 (0.42–14.9)
Azathioprine ever	0.39 (0.11–1.38)	0.49 (0.12–1.97)
Methotrexate ever	2.13 (0.73–6.23)	2.78 (0.90–8.59)
Mycophenolate ever	0.64 (0.18–2.28)	0.85 (0.19–3.78)
Antimalarial ever	0.33 (0.10–1.06)	0.28 (0.09–0.90)
Nonmelanoma skin, 10 events		
Age at SLE diagnosis, years	1.08 (1.04–1.13)‡	1.06 (1.02–1.11)‡
Female	0.29 (0.07–1.12)	0.65 (0.14–3.02)
White race/ethnicity	9.55 (1.21–75.6)‡	5.79 (0.64–52.1)
Top quartile SLE activity ever	0.15 (0.02–1.22)	0.10 (0.01–0.92)
Smoking ever	2.68 (0.75–9.49)	1.72 (0.44–6.67)
Steroids ever	0.90 (0.19–4.27)	0.66 (0.11–4.15)
Cyclophosphamide ever	4.01 (1.13–14.3)‡	15.3 (3.03–77.5)‡
Azathioprine ever	0.68 (0.18–2.64)	0.80 (0.16–3.86)
Methotrexate ever	2.05 (0.53–7.98)	3.58 (0.78–16.4)
Mycophenolate ever	2.04 (0.55–7.56)	2.63 (0.58–12.0)
Antimalarial ever	0.22 (0.06–0.84)	0.23 (0.05–0.95)
Biologic ever	1.24 (0.15–10.2)	1.06 (0.10–11.1)
Lung cancer, 7 events		
Female	0.09 (0.02–0.42)‡	0.18 (0.04–0.86)‡
Top quartile SLE activity ever	0.24 (0.03–1.98)	0.31 (0.02–4.06)
Cigarettes ≥15/day	11.7 (2.61–52.2)‡	6.64 (1.43–30.9)‡
Steroids ever	0.50 (0.10–2.61)	0.66 (0.10–4.52)
Azathioprine ever	1.08 (0.24–4.82)	2.16 (0.36–13.0)
Mycophenolate ever	0.39 (0.05–3.31)	0.46 (0.04–5.84)
Biologic ever	1.32 (0.16–11.2)	2.89 (0.20–42.3)
Hematologic cancer, 6 events		
Age at SLE diagnosis	1.06 (1.01–1.11)‡	1.06 (1.00–1.13)‡
Female	0.59 (0.07–5.01)	0.84 (0.09–7.70)
Top quartile SLE activity ever	2.97 (0.54–16.2)	7.14 (1.13–45.3)‡
Cigarettes ≥15/day	4.39 (0.80–24.0)	2.83 (0.49–16.4)
Steroids ever	0.44 (0.08–2.41)	0.52 (0.08–3.42)
Azathioprine ever	0.30 (0.04–2.60)	0.29 (0.03–2.81)
Methotrexate ever	0.91 (0.11–7.77)	0.67 (0.07–6.34)
Mycophenolate ever	0.54 (0.06–4.67)	0.50 (0.05–5.18)
Biologic ever	1.32 (0.16–11.2)	2.89 (0.20–42.3)

* 95% CI = 95% confidence interval; SLE = systemic lupus erythematosus.
† Adjusted for all variables shown; disease activity, smoking, and all drug variables were time dependent. All hematologic and lung cancer cases were smokers, all were White, and none were exposed to cyclophosphamide, so race/ethnicity and cyclophosphamide were not evaluated in those models. All lung cancers had been exposed to antimalarials.
‡ Statistically significant.

As mentioned, all lung cancer patients were smokers, so we could not calculate effects for ever/never smoking, but we were able to calculate a hazard ratio of approximately 7 for heavier smoking and lung cancer (15 cigarettes a day or more). Lung cancer was also more common in SLE patients of male sex and older age at SLE diagnosis (Table 3). Interestingly, none of the lung cancer cases had been exposed to cyclophosphamide or methotrexate, and all had been exposed to antimalarial agents for at least 5 years; this fact precluded us from being able to calculate specific estimates of risk for lung cancer for these agents.

Multivariate analyses of hematologic cancers produced relatively imprecise estimates of the effects of all exposures of interest (Table 3), aside from the effect of older age at SLE onset, which remained a risk factor across all analyses. All patients with hematologic malignancies were White and smokers, and none had received cyclophosphamide, precluding study of these variables as hematologic cancer risk factors in SLE. There was no clear link with any other drug and hematologic cancer. The unadjusted hematologic cancer HR for ever having smoked ≥20 cigarettes per day (prior to the index date of cancer) was 5.96 (95% confidence interval [95% CI] 1.09–32.5), but in the models in Table 3 where smoking was dichotomized at 15 cigarettes per day, as it was in lung cancer, the 95% CIs for smoking and hematologic cancer included the null value. There was a positive association between hematologic cancer and SLE activity (ever scoring in the highest quartile of adjusted mean SLEDAI-2K scores over time: univariate and adjusted analyses) (Table 3), but no other clear associations between hematologic cancer risk and clinical factors were found.

DISCUSSION

We present novel data from a large, multicenter inception SLE cohort, suggesting how different cancer types in SLE may be associated with specific risk factors, including smoking, drug exposures, and disease activity. The first message that these data highlight is that cancers, especially lung cancer, are more likely to occur in patients who report past/current smoking. Our previous work with prevalent SLE patients also found that the most important risk factors associated with lung cancer risk were older age, male sex, and positive smoking history (8). In the current analyses, all of our lung cancer cases were ever smokers, thus precluding any estimate of the effect of this binary variable. However, we were able to illustrate that smoking ≥15 cigarettes a day was associated with approximately a 7-fold increased risk of lung cancer in SLE. This effect estimate is similar to a recent meta-analysis of the effects of smoking on lung cancer in the general population, in both men and women (9).

Previous assessment of cancer risk in SLE had also highlighted White race/ethnicity as a risk factor (10), which may reflect a decreased risk of certain cancer types (particularly breast) in women of non-White race/ethnicity (11). Among 824 White patients, 44 cancers occurred (5.3% [95% CI 4.0–7.1]); this proportion was numerically higher than the percentage in Black or Asian individuals, but the confidence intervals overlapped (6 cancers in 276 black patients, 2.2% [95% CI 1.0–4.7], versus 6

cancers in 255 Asian patients, 2.4% [95% CI 1.1–5.0]). The trend for higher overall cancer risk in White SLE patients did not quite reach statistical significance in our adjusted models. All of the lung and hematologic cancer cases in our analyses occurred in White patients, so that determining the effects of race/ethnicity in those specific analyses was impossible. Our analyses in prevalent SLE also suggested that White subjects with SLE appeared to have a higher overall cancer risk than those of other race/ethnicity, though the heightened risk of lymphoma in SLE seemed fairly consistent across race/ethnicity (12).

Male sex and older age of SLE onset were risk factors for cancer risk across most cancer types. This finding may be, at least in part, because these demographic groups are at greater cancer risk in the general population. However, further study of cancer risk in these potentially vulnerable SLE populations would be of interest, to determine whether longer windows of observation result in the same findings and/or identify any additional risk factors.

A comparison of cancer rates in SLE to the general population was not the purpose of our study, but our 2013 publication showed that the standardized incidence ratio for cancer in male lupus patients (that is, cancer risk compared to the age-matched male general population) was 1.08 (95% CI 0.87–1.24); the point estimate is consistent with a relatively small increased cancer risk in male patients with SLE versus the male general population, but the 95% CI includes the null value. Since SLE patients are predominantly female, we were able, in that study, to show that the standardized incidence ratio in female lupus patients (cancer risk relative to general population females) was 1.15 (95% CI 1.05–1.24) (13). Longer follow-up would also allow more precise estimation of the effect of multiple sequential or combined immunosuppressive drug exposures and new drug exposures, including biologic therapies (for example belimumab, which was only approved for use in Europe, Canada, and the US in 2011).

In our study, the only cancer type for which cyclophosphamide appeared to be a risk factor was nonmelanoma skin cancer. Nonmelanoma skin cancers are well known as being possibly triggered by immunosuppressive drugs, for example in organ transplant populations (14). Cyclophosphamide specifically has been implicated as a risk factor for nonmelanoma skin cancer in vasculitis patients (15). The adverse effects of cyclophosphamide suggest that additional efforts are needed to understand how best to use this drug (e.g., with lower doses and shorter courses) and to develop alternative drugs for serious SLE manifestations. On the other hand, only 3 of 164 patients (1.8%) exposed to cyclophosphamide developed cancer over the current interval, which is a relatively small number. Interestingly, we did not observe any bladder cancers in our cohort, given concerns of cyclophosphamide-induced bladder cancer in vasculitis patients (16); however, bladder is a rare malignancy type, and thus completely ruling out associations with cyclophosphamide and rarer cancer types in SLE may require much longer follow-up. Putative associations between oncogenic viruses and nonmelanoma skin cancer (17) might be augmented in patients treated with immunosuppressants, including cyclophosphamide; some researchers suggest this link as a mechanism for the higher risk in SLE of other cancers (e.g., hepatobiliary, vulvovaginal) (18).

In SLE there is potential for further complex interactions between drugs and clinical variables like photosensitivity, which in the general population may put persons at risk for nonmelanoma skin cancer (19). For example, though SLE patients may be more sensitive than the general population to sun exposure (and hence theoretically to skin cancer), use of sunscreen by SLE patients might limit their ultraviolet ray exposure. In addition, chronic skin inflammation is itself a nidus for the development of nonmelanoma skin cancer (20); the apparently lower risk for nonmelanoma skin cancer in SLE patients receiving antimalarial agents might be related to its effects on controlling many forms of cutaneous lupus manifestations. The negative association between higher SLE activity and nonmelanoma skin cancer could hypothetically be because severe disease causes patients to be more adherent with antimalarials and/or photoprotection. Alternatively, some have suggested that the immune system's activity in deleting abnormal cells may be protective against cancer in SLE (21). These hypotheses remain to be tested.

Negative associations between antimalarial use and cancer (as was seen in our study, concerning breast and nonmelanoma skin cancer) were suggested in an earlier study of SLE patients (22), though this result has not necessarily been found in other conditions (such as rheumatoid arthritis, where antimalarial use is less common than in SLE) (23). There is a significant literature on the effects of antimalarial drugs on cancer in nonrheumatic disease, including 1 study showing that chloroquine inhibited proliferation and autophagy in estrogen-receptor positive breast cancer cells (from non-SLE patients) (24,25). Since all of the lung cancer cases in our study had been exposed to antimalarial agents, we were unable to calculate specific estimates of lung cancer risk, but a recent study suggested that hydroxychloroquine may suppress lung cancer cell growth (and make the cells more sensitive to chemotherapy) (26). Hydroxychloroquine has even been employed as an adjunct in phase 1 studies of lung cancer therapy (27), although its usefulness remains unclear.

No observational study can ever prove causality. In fact, no single study is likely, on its own, to prove causality. However, randomized controlled trials are often considered the best way to examine cause-effect relationships between an intervention and outcome. If in the future we are able to perform long-term pragmatic trials assigning SLE patients to different regimens (e.g., low-dose or short-term hydroxychloroquine as opposed to long-term use), that might be the best way to provide evidence of a presumptive causal relationship. Given how useful hydroxychloroquine is to SLE patients, that kind of study would be difficult to conduct. For many years, hematologic cancer risk in SLE has been of particular interest, given previous hypotheses that both

disease activity and drugs could potentially contribute to risk of these events.

In 2 prior very large multicenter studies of prevalent SLE patients, we found signals for an increased risk of hematologic cancers related to SLICC/ACR damage index scores (28), which have been shown to correlate with cumulative lupus disease activity (29), and also with cyclophosphamide (30). Although no drug was clearly associated with hematologic cancers in our current multivariate analyses, the relatively few events produced rather imprecise estimates of cancer risk related to most of the drug exposures of interest. Although none of the hematologic cancers occurred in cyclophosphamide-exposed patients, we did see an association between high disease activity and hematologic cancer risk in the fully adjusted analyses. Not unexpectedly, given that the risk of most hematologic cancers is higher in older individuals, older age at SLE onset was also a predictor of hematologic malignancies in our sample. Additional follow-up of our inception cohort would be essential to further delineate effects of medications and disease activity for hematologic cancers overall, and potentially for specific types, such as non-Hodgkin's lymphoma, the most common hematologic cancer in SLE.

In our analyses, we did not calculate standard incidence ratios of cancer risk in SLE compared to the general population, since general population cancer rates are generated from cancer registry data, and our means of cancer incidence ascertainment was by physicians recording events at annual visits, confirmed by review of charts, including pathology reports where available. In some jurisdictions, certain cancers (e.g., nonmelanoma skin, cervix) are often incompletely recorded by cancer registries. Our ascertainment methods were perhaps more likely to pick up such cancers than cancer registry data. This possibility should not raise a problem for the analyses of cancer risk factors in SLE (the focus of the current article). However, attempts to compare physician-reported cancer events (in SLE) to cancer registry data (i.e., general population cancer rates) would potentially be problematic due to differential misclassification error of the outcome. In previous analyses of SLE cohorts, including a mix of prevalent and incident patients, there have been consistent, clear increased risks of hematologic cancer and lung cancer. Considering the age and sex distribution of our patients, and their countries of origin, the number of hematologic cancer cases observed in the current cohort are each approximately 3-fold higher than might be expected, which is compatible with our own earlier estimates.

In summary, in this large inception SLE cohort, we were able to see potential associations between cancer and smoking, demographic characteristics, and clinical factors. As expected, older age was associated with cancer overall, as well as with the most common cancer subtypes. As in the general population, female patients with SLE have fewer events than male patients (for cancer risk overall, as well as lung cancer specifically). Smoking is a key modifiable risk factor for lung cancer in SLE. For breast and nonmelanoma skin cancer, antimalarial drugs were associated with lower risk. No other drug effects were clearly seen, but confidence intervals around many estimates were relatively imprecise. SLE activity was associated with increased hematologic cancer risk and decreased nonmelanoma skin cancer risk. Further study of cancer risk in this inception cohort would be of interest, to determine whether longer windows of observation result in different findings, particularly in relation to drug exposures and disease activity.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Bernatsky had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bernatsky, Ramsey-Goldman, Urowitz, Hanly, Gordon, Clarke.

Acquisition of data. Bernatsky, Ramsey-Goldman, Urowitz, Hanly, Gordon, Petri, Ginzler, Wallace, Bae, Romero-Diaz, Dooley, Peschken, Isenberg, Rahman, Manzi, Jacobsen, Lim, van Vollenhoven, Nived, Kamen, Aranow, Ruiz-Irastorza, Sánchez-Guerrero, Gladman, Fortin, Alarcón, Merrill, Kalunian, Ramos-Casals, Steinsson, Zoma, Askanase, Khamashta, Bruce, Inanc, Clarke.

Analysis and interpretation of data. Bernatsky, Ramsey-Goldman, Urowitz, Hanly, Gordon, Clarke.

REFERENCES

1. Egiziano G, Bernatsky S, Shah AA. Cancer and autoimmunity: harnessing longitudinal cohorts to probe the link. Best Pract Res Clin Rheumatol 2016;30:53–62.
2. Kidane D, Chae WJ, Czochor J, Eckert KA, Glazer PM, Bothwell AL, et al. Interplay between DNA repair and inflammation, and the link to cancer. Crit Rev Biochem Mol Biol 2014;49:116–39.
3. Van den Brand JA, van Dijk PR, Hofstra JM, Wetzels JF. Cancer risk after cyclophosphamide treatment in idiopathic membranous nephropathy. Clin J Am Soc Nephrol 2014;9:1066–73.
4. Parikh-Patel A, White RH, Allen M, Cress R. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. Cancer Causes Control 2008;19:887–94.
5. Urowitz MB, Gladman DD. The SLICC inception cohort for atherosclerosis. Curr Rheumatol Rep 2008;10:281–5.
6. Hochberg MC, for the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
7. Ibañez D, Urowitz MB, Gladman DD. Summarizing disease features over time: I. Adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. J Rheumatol 2003;30:1977–82.
8. Bernatsky S, Ramsey-Goldman R, Petri M, Urowitz MB, Gladman DD, Fortin PR, et al. Smoking is the most significant modifiable lung cancer risk factor in systemic lupus erythematosus. J Rheumatol 2018;45:393–6.
9. O'Keefe LM, Taylor G, Huxley RR, Mitchell P, Woodward M, Peters SA. Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis. BMJ Open 2018;8:e021611.
10. Ramsey-Goldman R, Mattai SA, Schilling E, Chiu YL, Alo CJ, Howe HL, et al. Increased risk of malignancy in patients with systemic lupus erythematosus. J Investig Med 1998;46:217–22.
11. Kinyemiju T, Moore JX, Pisu M. Mediating effects of cancer risk factors on the association between race and cancer incidence:

analysis of the NIH-AARP Diet and Health Study. Ann Epidemiol 2018;28:33–40.
12. Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Urowitz M, et al. Race/ethnicity and cancer occurrence in systemic lupus erythematosus. Arthritis Rheum 2005;53:781–4.
13. Bernatsky S, Ramsey-Goldman R, Labrecque J, Joseph L, Boivin JF, Petri M, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun 2013;42:130–5.
14. Chung EY, Palmer SC, Strippoli GF. Interventions to prevent non-melanoma skin cancers in recipients of a solid organ transplant: systematic review of randomized controlled trials. Transplantation 2019;103:1206–15.
15. Faurschou M, Sorensen IJ, Mellemkjaer L, Loft AG, Thomsen BS, Tvede N, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol 2008;35:100–5.
16. King C, Harper L. Avoidance of harm from treatment for ANCA-associated vasculitis. Curr Treatm Opt Rheumatol 2017;3:230–43.
17. Dreyer L, Faurschou M, Mogensen M, Jacobsen S. High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: a long-term followup study in a Danish cohort. Arthritis Rheum 2011;63:3032–7.
18. Baez CF, Gonçalves MT, da Rocha WM, Magalhães de Souza L, Savassi-Ribas F, de Oliveira Almeida NK, et al. Investigation of three oncogenic epitheliotropic viruses shows human papillomavirus in association with non-melanoma skin cancer. Eur J Clin Microbiol Infect Dis 2019;38:1129–33.
19. Clouser MC, Harris RB, Roe DJ, Saboda K, Ranger-Moore J, Duckett L, et al. Risk group, skin lesion history, and sun sensitivity reliability in squamous cell skin cancer progression. Cancer Epidemiol Biomarkers Prev 2006;15:2292–7.
20. Zaalberg A, Moradi Tuchayi S, Ameri AH, Ngo KH, Cunningham TJ, et al. Chronic inflammation promotes skin carcinogenesis in cancer-prone discoid lupus erythematosus. J Invest Dermatol 2019;139:62–70.
21. Dey D, Kenu E, Isenberg DA. Cancer complicating systemic lupus erythematosus: a dichotomy emerging from a nested case-control study. Lupus 2013;22:919–27.
22. Ruiz-Irastorza G, Ugarte A, Egurbide MV, Garmendia M, Pijoan JI, Martinez-Berriotxoa A, et al. Antimalarials may influence the risk of malignancy in systemic lupus erythematosus. Ann Rheum Dis 2007;66:815–7.
23. Bernatsky S, Clarke A, Suissa S. Antimalarial drugs and malignancy: no evidence of a protective effect in rheumatoid arthritis. Ann Rheum Dis 2008;67:277–8.
24. Yang W, Hosford SR, Traphagen NA, Shee K, Demidenko E, Liu S, et al. Autophagy promotes escape from phosphatidylinositol 3-kinase inhibition in estrogen receptor-positive breast cancer. FASEB J 2018;32:1222–35.
25. Cook KL, Wärri A, Soto-Pantoja DR, Clarke PA, Cruz MI, Zwart A, et al. Hydroxychloroquine inhibits autophagy to potentiate antiestrogen responsiveness in ER+ breast cancer. Clin Cancer Res 2014;20:3222–32.
26. Li Y, Cao F, Li M, Li P, Yu Y, Xiang L, et al. Hydroxychloroquine induced lung cancer suppression by enhancing chemo-sensitization and promoting the transition of M2-TAMs to M1-like macrophages. J Exp Clin Cancer Res 2018;37:259.
27. Goldberg SB, Supko JG, Neal JW, Muzikansky A, Digumarthy S, Fidias P, et al. A phase I study of erlotinib and hydroxychloroquine in advanced non-small cell lung cancer. J Thorac Oncol 2012;7:1602–8.
28. Bernatsky S, Ramsey-Goldman R, Joseph L, Boivin JF, Costenbader KH, Urowitz MB, et al. Lymphoma risk in systemic lupus: effects of disease activity versus treatment. Ann Rheum Dis 2014;73:138–42.
29. Eder L, Urowitz MB, Gladman DD. Damage in lupus patients: what have we learned so far? Lupus 2013;22:1225–31.
30. Bernatsky S, Joseph L, Boivin JF, Gordon C, Urowitz M, Gladman D, et al. The relationship between cancer and medication exposures in systemic lupus erythaematosus: a case-cohort study. Ann Rheum Dis 2008;67:74–9.

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Cervical Cancer Screening in Women With Systemic Lupus Erythematosus

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Objective. To determine rates of cervical cancer screening and associated abnormal results in women with systemic lupus erythematosus (SLE).

Methods. We identified women with an initial diagnosis of SLE in the MarketScan Commercial Claims and Encounters Database from 2001 to 2014. Cervical cancer screening rates and associated diagnostic claims within 3 years of the initial claim were determined. Multivariable logistic regression was performed to evaluate the association of screening with lupus treatment. A matched logistic regression analysis was conducted to compare screening rates to those in age-matched women without connective tissue disease.

Results. We included 4,316 women with SLE. Screening rates were higher in women with SLE than in general controls (73.4% versus 58.5%; $P < 0.001$). Factors associated with decreased screening included recent time (odds ratio [OR] 0.70 [95% confidence interval (95% CI)] 0.55–0.89) (2012–2014 compared to 2001–2005), age ≥61 years (OR 0.27 [95% CI 0.18–0.39]), comorbidity score ≥2 (OR 0.71 [95% CI 0.6–0.83]), corticosteroid use (OR 0.77 [95% CI 0.61–0.97]), and use of immunosuppressants (OR 0.80 [95% CI 0.69–0.94]). Abnormal pathology result claims were more common in women with SLE than in general controls (12.3% versus 9.8%; $P < 0.001$).

Conclusion. Though with higher rates than the general cohort, over 25% of the patients with SLE were not screened, and screening rates seem to be decreasing over time. Patients with SLE are at higher risk of abnormal cervical screening test results than controls, supporting the need for regular screening.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is more prevalent in women and carries an increased risk for both viral illnesses and malignancies (1–6). This increased risk is thought to be related to inherent abnormalities in the innate and adaptive immune systems along with chronic immunosuppression. Women with SLE have an increased risk of cervical cancer, a disease caused primarily by the human papilloma virus (HPV) (1,4,5,7–9). Several studies have shown that immunosuppressive therapies, especially cyclophosphamide and glucocorticoids, are also associated with an increased risk of cervical cancer (8–10). This increased risk is recognized by the American Society of Colposcopy and Cervical Pathology (ASCCP). In 2019 the ASCCP recommended more frequent cervical cancer screening in women with SLE than in the general population, similar to what is recommended for HIV-infected patients (11). These recommendations are to perform an annual cervical cytology examination, and if 3 consecutive cytology test results are normal, perform cytology examinations every 3 years; if baseline co-testing results for HPV are negative with normal cytology results, screening can be performed every 3 years.

There is a paucity of knowledge in patterns of cervical cancer screening and determinants associated with cervical cancer screening in women with SLE. Our objectives were to determine in a large national claims database the proportion of women with SLE who underwent cervical cancer screening within 3 years of their initial lupus diagnosis claim, and to determine whether

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SIGNIFICANCE & INNOVATIONS

- Screening for cervical cancer in women with systemic lupus erythematosus has declined over time, and approximately 25% of women were not screened within 3 years of diagnosis.
- Women with lupus were less likely to be screened when receiving immunosuppressant therapies.
- Women with lupus had a higher rate of abnormal cervical screening results than controls.

screening rates were associated with immunosuppressive therapy. Screening in patients with SLE was compared to screening in women without connective tissue diseases and in women with diabetes mellitus, as age-matched controls. We also examined the frequency of abnormal cervical pathology claims in women with SLE compared to controls.

MATERIALS AND METHODS

We performed a retrospective cohort study analyzing claims of female beneficiaries, from the commercial Truven Health Analytics MarketScan Commercial Claims and Encounters Research database (12). This database consists of medical (inpatient and outpatient) and prescription claims for millions of individuals who have employer-sponsored private health insurance, and also includes their spouses and dependents. MarketScan does not include patients who are on Medicaid, are uninsured, or have other less common private insurance plans. We initially identified women who had any lupus (International Classification of Diseases [ICD] version 9 diagnosis code 710.0 or ICD version 10 diagnosis code M32.xx but not M32.0) claims between January 1, 2000 and December 31, 2016 for cohort selection. Inclusion criteria for our final cohort of women with lupus were: 1) age between 21 and 64 years at the first lupus claim; 2) at least 3 lupus claims within 2 years, with the first and last lupus claims >90 days apart, between 2001 and 2014; data were available up to 2016, and we included patients with first lupus claims up to 2014 to ensure follow-up of at least 2 years after the first lupus claim; 3) coverage for at least 12 months before the date of the first lupus claim with no lupus claims during that same period; this criterion was set to capture as many incident cases as possible, assuming that most patients with prevalent lupus would have at least 1 annual visit with a documented lupus claim; 4) at least 90 days of supply of 1 or more of the following antimalarial drugs between 3 months before and 2 years after the first lupus claim: hydroxychloroquine, chloroquine, or quinacrine; and 5) coverage for at least 2 years after the first lupus claim.

We excluded women who had 1) a claim for antimalarial drugs between 3 to 12 months before the first lupus claim, to increase the likelihood of recent disease onset; 2) 2 or more claims of 710.3/M33.xx (dermatomyositis), 710.1/M34.xx (systemic sclerosis), or 714.0/M05.xx/M06.xx (rheumatoid arthritis) within 1 year before and 2 years after the first lupus claim; and 3) any claim for hysterectomy (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24414/abstract) before the first lupus claim, or follow-up.

Outcome. We identified cervical cancer screening using diagnosis or procedure codes for Papanicolaou (Pap) smears and HPV testing (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24414/abstract) within 1 year before and 2 years after the first lupus claim. We included the year prior to lupus diagnosis because we assumed that if screening had been recently performed, it would be appropriate not to repeat it.

Codes were selected after review of various publications related to cervical cancer screening (13–15). Among women who had cervical cancer screening, results were categorized as abnormal if there were associated codes of abnormal cervical pathology as defined by the Healthcare Common Procedure Coding System (HCPCS) codes (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24414/abstract) between the year before and 2 years after the first lupus claim.

Covariates. From the claims file, we included the year of first lupus claim (2001–2014); age at first lupus claim (21–30, 31–40, 41–50, 51–60, or 61–64 years); Deyo's modification of Charlson's comorbidity index score (0–1, ≥2) (16); insurance type, including preferred provider organization, health maintenance organization (HMO), or other; and region of residence (northeast, north central, south, west, and unknown). From the prescription file we identified women who had claims for glucocorticoids between 1 year prior to and 2 years after the first lupus claim by using both prescription files and HCPCS J codes. The glucocorticoids included were betamethasone, cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone. Administration routes considered were oral, intramuscular, subcutaneous, and intravenous (IV) (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24414/abstract).

Patients were categorized into 2 groups according to the duration of corticosteroid therapy: 0–89 days and ≥90 days. We also identified therapy with immunosuppressive and biologic agents, including rituximab, belimumab, azathioprine, methotrexate, leflunomide, cyclophosphamide, mycophenolate, cyclosporine, and tacrolimus, using claims with prescription data and HCPCS J codes (see Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24414/abstract). We included oral, IV (hospital and outpatient administered), subcutaneous, and intramuscular administration routes. Dosage intervals and mode of administration were used to established the duration

of treatment, grouped into 0–89 days and no IV administration, and ≥90 days or IV administration. For oral drugs, we only included patients who had been dispensed 60 tablets over 90 days.

Matched controls. We matched SLE cases by date of birth with 2 control cohorts: women without connective tissue disease and not on antimalarial drugs (general controls); and women without connective tissue disease and not on antimalarial drugs and with at least 2 diabetes mellitus claims 7 or more days apart (diabetes mellitus cohort). The codes are shown in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24414/abstract. We included a diabetes mellitus control cohort to evaluate 2 practices in patients with a chronic nonrheumatic disease.

For these 2 control cohorts, the inclusion criteria were coverage for at least 3 years in the database between 2001 and 2015 and ages between 21 and 63 years. Cases were randomly matched with controls, with a maximum of a 1:20 ratio. The inception follow-up date for the controls was the date of the first lupus claim for their matched case.

Statistical analysis. Descriptive statistics (means, medians, and frequencies) were calculated. We compared sociodemographic and clinical characteristics between groups using chi-square tests and trend tests when appropriate. Multivariable logistic regression was performed to evaluate the association between baseline characteristics and cervical cancer screening in women with SLE, forcing all variables into the model. Results were expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs).

To compare cases and controls, we performed matched logistic regression, including all baseline characteristics as covariates. We included group (case versus control) as the primary independent

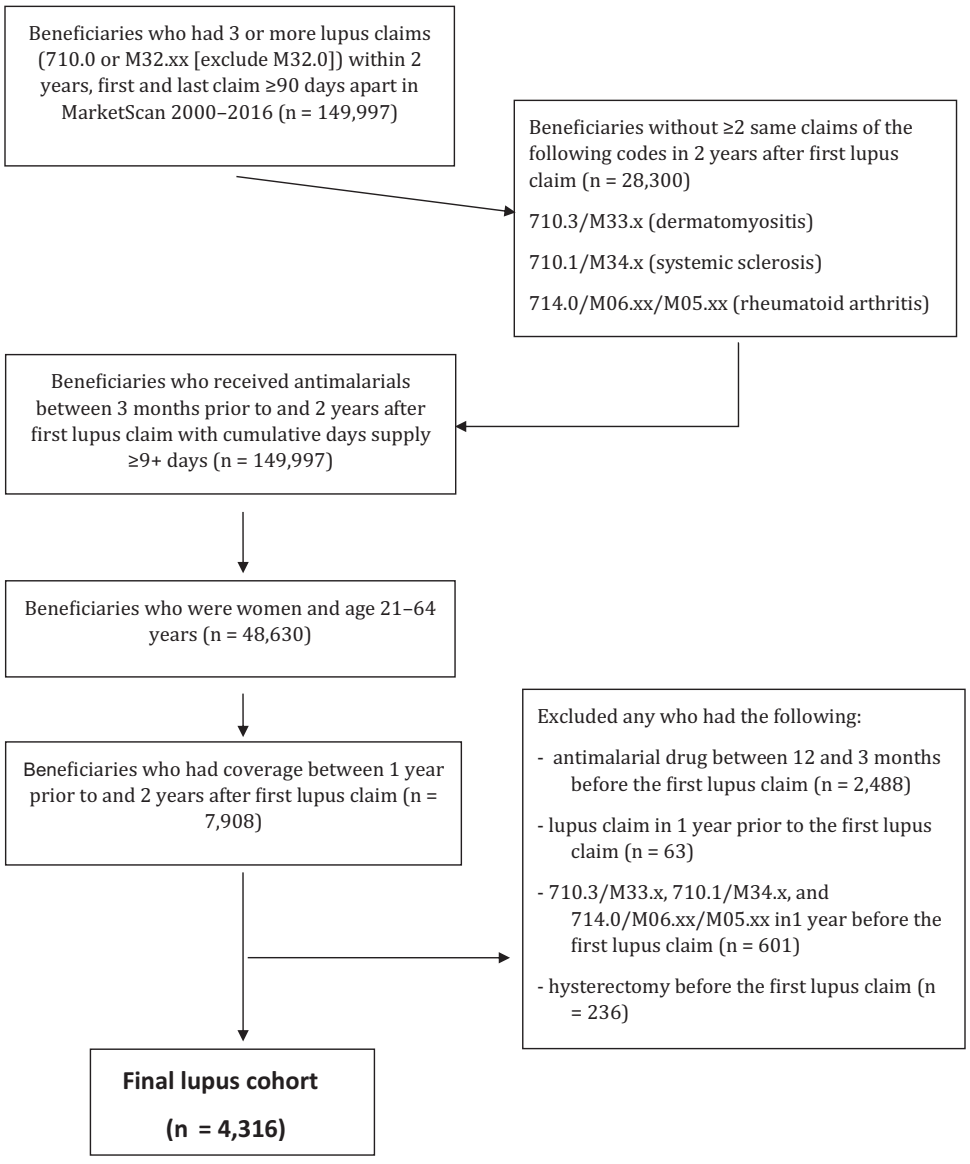

Figure 1. Flow chart of cohort selection.

variable and adjusted for year of claim groups (2001–2005, 2006–2007, 2008–2009, 2010–2011, 2012–2014), age groups (21–30, 31–40, 41–50, 51–60, 61–64 years), comorbidity score (0–1, ≥2), and insurance type. We tested interactions between group (case or control) and covariates. All analyses were conducted using SAS software, version 9.3. This study was exempt by our Institutional Review Board, because it only used de-identified claims data.

RESULTS

We included a total of 4,316 women with SLE (Figure 1). The median age at first lupus claim was 45 years. Of these women, 3,165 (73.4% [95% CI 72.0–74.6]) underwent cervical cancer screening within the 3-year window of the first lupus claim (1 year prior to and 2 years after the claim). Table 1 summarizes the baseline characteristics in patients with and without cervical cancer screening. Older patients, those with more comorbidities, and those receiving glucocorticoids or immunosuppressants were less likely to undergo cervical cancer screening than their counterparts. The temporal trend of cervical cancer screening decreased over time from 75.6% in 2004 to 69.9% in 2015 (P for trend = 0.003.)

We conducted a multivariate logistic regression model to evaluate the association of screening in patients with SLE with covariates (Table 2). The following factors were associated with decreased cervical cancer screening: year of first lupus claim, 2012–2014 versus 2001–2005 (OR 0.70 [95% CI 0.55–0.89], $P < 0.001$); older age, 61–64 versus 21–30 years (OR 0.27 [95% CI 0.18–0.39], $P < 0.001$); comorbidity score of ≥2 versus 0–1 (OR 0.71 [95% CI 0.6–0.83], $P < 0.001$); use of glucocorticoids for >90 days versus use for 0–89 days (OR 0.77 [95% CI 0.61–0.97],

Table 1. Patient characteristics at first claim according to cervical cancer screening utilization*

Characteristics	Total (n = 4,316)	No screening (n = 1,151)	Screening (n = 3,165)	P†	P for trend
Year of first lupus claim					
2001–2005	507 (11.7)	122 (24.1)	385 (75.9)	0.019	0.003
2006–2009	1,013 (23.5)	252 (24.9)	761 (75.1)	–	–
2010–2011	1,293 (30)	334 (25.8)	959 (74.2)	–	–
2012–2014	1,503 (34.8)	443 (29.5)	1,060 (70.5)	–	–
Age at first lupus claim, years					
Median	45	50	43	–	–
21–30	490 (11.4)	74 (15.1)	416 (84.9)	<0.001	<0.001
31–40	1,081 (25)	198 (18.3)	883 (81.7)	–	–
41–50	1,290 (29.9)	334 (25.9)	956 (74.1)	–	–
51–60	1,237 (28.7)	458 (37)	779 (63)	–	–
61–64	218 (5.1)	87 (39.9)	131 (60.1)	–	–
Deyo comorbidity index					
0–1	3,418 (79.2)	836 (24.5)	2,582 (75.5)	<0.001	–
≥2	898 (20.8)	315 (35.1)	583 (64.9)	–	–
Insurance					
PPO	2,514 (58.2)	651 (25.9)	1,863 (74.1)	0.32	–
HMO	712 (16.5)	186 (26.1)	526 (73.9)	–	–
Other	993 (23)	287 (28.9)	706 (71.1)	–	–
Unknown	97 (2.2)	27 (27.8)	70 (72.2)	–	–
Glucocorticoids, days					
0–89 days	529 (12.3)	112 (21.2)	417 (78.8)	0.002	–
≥90 days	3,787 (87.7)	1,039 (27.4)	2,748 (72.6)	–	–
Biologic medications and other immunosuppressive agents, days supply or IV‡					
0–89 days, no IV	3,250 (75.3)	829 (25.5)	2,421 (74.5)	0.003	–
≥90 days or IV	1,066 (24.7)	322 (30.2)	744 (69.8)	–	–
Biologic medications, days supply or IV					
0–89 days, no IV	4,201 (97.3)	1,114 (26.5)	3,087 (73.5)	0.18	–
≥90 days or IV	115 (2.7)	37 (32.2)	78 (67.8)	–	–
Other immunosuppressive agents, days supply or IV					
0–89 days, no IV	3,300 (76.5)	847 (25.7)	2,453 (74.3)	0.007	–
≥90 days or IV	1,016 (23.5)	304 (29.9)	712 (70.1)	–	–

* Values are the number (%) unless indicated otherwise. HMO = health maintenance organization; IV = intravenous; PPO = preferred provider organization.
† P value by chi-square test.
‡ Biologic medications included rituximab (IV) and belimumab (IV or subcutaneous). Other immunosuppressive agents included azathioprine, cyclophosphamide, cyclosporine, leflunomide, methotrexate, mycophenolate, and tacrolimus.

Table 2. Multivariable logistic regression for cervical cancer screening in women with SLE*

Variable	Odds ratio (95% CI)	*P*
Year of first lupus claim		
2001–2005	1	–
2006–2009	0.94 (0.73–1.22)	0.65
2010–2011	0.85 (0.66–1.09)	0.20
2012–2014	0.70 (0.55–0.89)	0.003
Age at first lupus claim, years		
21–30	1	–
31–40	0.75 (0.56–1.01)	0.06
41–50	0.49 (0.37–0.64)	<0.001
51–60	0.29 (0.22–0.39)	<0.001
61–64	0.27 (0.18–0.39)	<0.001
Deyo comorbidity index		
0–1	1	–
≥2	0.71 (0.6–0.83)	<0.001
Insurance		
PPO	1	–
HMO	0.90 (0.74–1.1)	0.31
Other	0.86 (0.73–1.02)	0.09
Unknown	0.84 (0.52–1.34)	0.46
Glucocorticoids, days		
0–89 days	1	–
≥90 days	0.77 (0.61–0.97)	0.026
Biologic medications, other immunosuppressive agents, days supply or IV†		
0–89 days, no IV	1	–
≥90 days or IV	0.80 (0.69–0.94)	0.008
Region		
Northeast	1	–
North central	0.72 (0.56–0.92)	0.01
South	0.77 (0.61–0.96)	0.02
West	0.69 (0.54–0.9)	0.005

* 95% CI = 95% confidence interval; HMO = health maintenance organization; IV = intravenous; PPO = preferred provider organization; SLE = systemic lupus erythematosus.
† Biologic medications included rituximab (IV) and belimumab (IV or subcutaneous). Other immunosuppressive agents included azathioprine, cyclophosphamide, cyclosporine, leflunomide, methotrexate, mycophenolate, and tacrolimus.

P = 0.026); and use of biologic or other immunosuppressant drugs (OR 0.80 [95% CI 0.69–0.94], *P* = 0.008). Insurance type was not associated with different screening rates.

The general control cohort included 82,723 women. Results of the multivariable conditional logistic regression are shown in Table 3. Women with SLE were more likely to undergo cervical cancer screening than the general controls (OR 2.2 [95% CI 2.03–2.36], *P* < 0.001) after adjusting for covariates. The following factors were associated with decreased cervical cancer screening across the entire group: more recent years (OR 0.49 [95% CI 0.47–0.52], *P* < 0.001), older ages, most notably 61–64 years (OR 0.38 [95% CI 0.35–0.42], *P* < 0.0001), increased comorbidities (OR 0.74 [95% CI 0.67–0.82]), HMO insurance (OR 0.93 [95% CI 0.89–0.97], *P* < 0.001), and region, most notably West (OR 0.55 [95% CI 0.53–0.58], *P* < 0.001). A significant interaction between group (case or control) and year of claim was observed. For women with SLE, the screening rates were stable at approximately 74–76% from 2001 to 2011, and decreased to 70.5% in 2012–2014. For women in the general control cohort, the screening rate decrease was larger, from 69% in 2001–2005 to 59% in 2006–2009, to 56.5% in 2010–2011, and to 53% in 2012–2014. No significant interactions were observed for the other covariates. Similar findings were found when comparing the SLE and diabetes mellitus cohorts, with the exception of insurance. Models with full covariates are included in Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24414/abstract.

We also examined changes in screening strategies over time, with statistically significant increases in Pap and HPV co-testing for all 3 cohorts (Table 4). For the lupus cohort, changes in screening rates over time according to age are shown in Supplementary Figures 1 and 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24414/abstract. Overall declines in any testing were observed in more recent years for all age groups. Increases in co-testing were observed for all age groups.

Table 5 shows the prevalence of abnormal cervical pathology results claims in all 3 cohorts. Women with SLE had more abnormal claims (12.3%) than the general (9.8%) or diabetes mellitus (9.0%) controls (*P* < 0.001). Among women with lupus, 14.6% of those who received immunosuppressant agents with or without glucocorticoids had abnormal results, compared to 11.5% of those who received glucocorticoids only, and 12.7% of those who did not receive either of the above during follow-up (*P* = 0.09) (see Supplementary Table 4, available on the *Arthritis Care & Research*

Table 3. Cervical cancer screening in cases and controls after multivariable adjustment*

Variable	No.	Screening rate, %	OR (95% CI)†	*P*
General control	82,723	58.5	1	–
Lupus	4,316	73.3	2.19 (2.03–2.36)	<0.001
Diabetes mellitus control	81,830	56.2	1	–
Lupus	4,092	73.3	2.44 (2.27–2.63)	<0.001

* 95% CI = 95% confidence interval; OR = odds ratio.
† Multivariable conditional logistic regression models were adjusted for year of first lupus claim, age at first lupus claim, comorbidity, insurance, employee relation, and region.

Table 4. Types of cervical screening methods in cases and controls over time*

Cohort, year of screening	Screening method			*P*
	Pap + HPV	Pap only	HPV only	
Lupus				
2000–2005	38 (9)	386 (91)	0 (0)	<0.001
2006–2007	73 (32.4)	152 (67.6)	0 (0)	–
2008–2009	249 (39)	387 (60.7)	2 (0.3)	–
2010–2011	406 (45)	496 (55)	0 (0)	–
2012–2014	495 (55)	398 (44.2)	7 (0.8)	–
2015–2016	41 (53.9)	35 (46.1)	0 (0)	–
General control				
2000–2005	435 (7.4)	5,440 (92.5)	8 (0.1)	<0.001
2006–2007	1,115 (23.5)	3,625 (76.3)	10 (0.2)	–
2008–2009	5,774 (30)	13,408 (69.7)	64 (0.3)	–
2010–2011	3,462 (34.5)	6,503 (64.8)	63 (0.6)	–
2012–2014	4,350 (46.1)	5,037 (53.4)	50 (0.5)	–
2015–2016	657 (50.1)	631 (48.1)	23 (1.8)	–
Diabetes mellitus control				
2000–2005	370 (6.5)	5,351 (93.5)	5 (0.1)	<0.001
2006–2007	970 (22.5)	3,326 (77.1)	19 (0.4)	–
2008–2009	6,014 (29.2)	14,494 (70.4)	72 (0.3)	–
2010–2011	3,057 (33.8)	5,947 (65.8)	37 (0.4)	–
2012–2014	4,256 (47.2)	4,717 (52.3)	44 (0.5)	–
2015–2016	451 (49.2)	455 (49.6)	11 (1.2)	–

* Values are the number (%) unless indicated otherwise. HPV = human papillomavirus; Pap = Papanicolaou.

website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24414/abstract).

DISCUSSION

To our knowledge, this is the first study to determine patterns of cervical cancer screening in the US in women with SLE, while considering concomitant immunosuppressive therapy. Our results indicate that while most patients with SLE undergo cervical cancer screening within 3 years of their first lupus claim, over one-fourth were not screened. Screening rates were nevertheless higher than those observed in the general and diabetes mellitus control cohorts, possibly suggesting awareness by patients and/or providers of increased risk for cervical cancer. Previous studies conducted in Italy and Sweden showed similar rates of cervical cancer screening in women with SLE compared to controls. These rates were lower than those observed in our study, with 55% in Sweden and 66% in Italy (9,17). Our cohort, as well as those in the European studies in countries with universal health care, had access to health insurance, so health insurance status was not a barrier. Our study did not include uninsured patients, who have been shown to have decreased rates of cervical cancer screening (18,19). Many women with lupus in the US are from minority ethnic groups, especially African American and Hispanic, and are frequently uninsured or underinsured, so conceivably cervical screening rates are much lower in these populations.

Overall cervical cancer screening rates in women with SLE decreased over time, from 76% in 2001–2005, to 70% in 2012–2014. The reasons for this decline are unclear, but the decline was also observed in the general population. A study by Watson et al, also using MarketScan data in the general population, reported a similar decline over time, which was more marked in women age 18–29 years and women age ≥40 years (13). A decline in cervical cancer screen rates may be secondary to increased time periods between screening as recommended by more recent guidelines, albeit increased time between cervical cancer screening should not apply to newly diagnosed patients with SLE if using screening guidelines as recommended by the ASCCP. Co-testing with Pap smears and HPV testing increased over time, which is consistent with HPV testing becoming more widely available in more recent years. We found that being older, having more comorbidities, and a longer duration of corticosteroid and/or immunosuppressant therapy were associated with decreased cervical cancer screening. Older age and comorbidities have also been associated with decreased screening for cervical cancer in the general population (13,20).

We suspect that patients on longer duration of glucocorticoids or on immunosuppressants have increased disease activity, which may contribute to less utilization of other health care services, including cervical cancer screening. This finding is

Table 5. Cervical abnormalities by method of screening*

Screening method	Lupus cases	General control	*P*, vs. lupus†	Diabetes control	*P*, vs. lupus†
Pap only, no.	1,854	34,644	0.10	34,290	0.006
Abnormal results	104 (5.6)	1,648 (4.8)	–	1,464 (4.3)	–
HPV only, no.	9	218	1.0	188	0.60
Abnormal results	0 (0)	21 (9.6)	–	21 (11.2)	–
Pap + HPV, no.	1,302	15,793	0.34	15,118	0.05
Abnormal results	286 (22.0)	3,294 (20.9)	–	2,979 (19.7)	–
All regardless of screening method, no.	3,165	50,655	<0.001	49,596	<0.001
Abnormal results	390 (12.3)	4,963 (9.8)	–	4,464 (9.0)	–

* Values are the number (%) unless indicated otherwise. HPV = human papillomavirus; Pap = Papanicolaou.
† *P* value by chi-square test or Fisher's exact test when appropriate.

concerning, because multiple studies have demonstrated an association between HPV infection and/or abnormal cervical cancer screening results in women with SLE receiving glucocorticoids or immunosuppressants, most commonly cyclophosphamide (7–9,21–24). More data are needed to determine the effect of chronic steroid use and various immunosuppressants and biologics on HPV, but this patient population should especially be considered for cervical cancer screening in clinical practice because they are likely at a higher risk of developing cervical cancer. One prospective study in Italy in 2011 interviewed 140 consecutive patients with SLE to determine cervical cancer screening habits (17). Researchers found that 66% of patients with SLE underwent appropriate cervical cancer screening, and there was no difference in abnormalities in cervical cancer screening between patients taking immunosuppressants or other disease-related variables. Notably, however, the study was not powered to detect a difference in patient characteristics associated with cervical cancer screening. A recent publication evaluated factors associated with cervical cancer screening adherence in patients with systemic sclerosis (25). This study also found that older patients were less likely to undergo routine screening; comorbidities, use of glucocorticoids or immunosuppressants, and secular trends were not examined.

We examined the use of different screening strategies and the frequency of abnormal results. We found that compared to both diabetes mellitus and general controls, women with SLE were more likely to have abnormal screening claims (12.3% versus 9.8% in general controls). These results provide further evidence to prior studies reporting that women with SLE have an increased risk of both abnormal cervical cancer screening results and cervical cancer (1,4,5,7,9). Our study, however, attempted to include primarily patients with newly diagnosed SLE (no claims in the year prior to inception), and abnormal screening results could have been present prior to the onset of SLE. Differences between patients and controls before disease onset could be secondary to socioeconomic or other unmeasured environmental cofounders (such as smoking) between these groups of women, or to abnormalities in the innate immune system that may occur prior to symptom onset in patients with SLE. Prospective longitudinal studies are needed to further explore these findings.

The strengths of this study include the fact that it was a large national community-based sample of 4,316 women with SLE, matched with 82,723 general controls and a long follow-up with the ability to study trends over time. To select a valid, well-specified cohort, we required that all women have several claims for lupus, be treated with antimalarials, and have no prior lupus diagnosis claims for a year to enhance capture of incident cases. However, we cannot completely rule out misclassification of lupus diagnosis. We were also able to examine treatment on the basis of prescription and drug administration claims. All women were required to have 2 years of continuous coverage for follow-up after the initial claim. We chose 2 separate control groups, 1 of women without connective tissue diseases, and the other including women with diabetes mellitus (to control for the potential effects of screening utilization of having a chronic disease that is nonrheumatic).

As with all claims-based studies, there are certain limitations inherent to this design. The MarketScan database is composed of insurance claims from private health insurers, large employers, and some government programs. Therefore, the data presented may not be generalizable to the population of women with SLE at large, especially those uninsured or underinsured. There are limitations when using ICD codes in administrative data studies. There may be information not reported (such as prior hysterectomy) that may have accounted for some patients not being screened. However, procedure codes are usually very reliable to establish utilization rates, and Pap smears and HPV testing are interventions that are typically billed. Most of the misclassification from claims codes relates to diagnosis of conditions, and for this reason, we required at least 3 claims with a lupus diagnostic code and treatment with hydroxychloroquine during follow-up, to ensure high specificity in case definition. As a result, we may have missed patients with mild disease who may not have been prescribed antimalarials. A major potential source of misclassification could be the determination of abnormal cervical findings, because these results are based on professional coding. We did find an increased frequency of abnormal results in women with SLE compared to controls, but these results cannot be considered as true prevalence rates, because many patients were not screened and there are practice-based variations in diagnostic coding among health care providers. However, an increased risk for abnormal cervical screening results and in the incidence of cervical cancer has been documented by others (1,4,5,7–9).

In conclusion, our data indicate that although more women with SLE undergo cervical cancer screening than do controls, a large proportion, over 25%, do not undergo cervical cancer screening within 3 years of their first lupus claim. We identified older age, increased comorbidities, and a longer duration of glucocorticoids and immunosuppressant therapy to be associated with decreased screening. These subgroups of women with SLE are likely to have the highest rates of cervical dysplasia and cancer, emphasizing the importance of adherence to guidelines for cervical cancer screening in this population. Future studies to identify barriers in cervical cancer screening and to increase adherence to guidelines are warranted. Finally, our results also provide evidence in support of prior findings suggesting that women with SLE carry an increased risk of abnormal cervical cancer screening results.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Suarez-Almazor had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lei, Zogala, Pundole, Zhao, Giordano, Hwang, Suarez-Almazor.

Acquisition of data. Bruera, Lei, Zogala, Suarez-Almazor.
Analysis and interpretation of data. Bruera, Lei, Zogala, Zhao, Rauh-Hain, Suarez-Almazor.

REFERENCES

1. Mendoza-Pinto C, Garcia-Carrasco M, Vallejo-Ruiz V, Mendez-Martinez S, Taboada-Cole A, Etchegaray-Morales I, et al. Incidence of cervical human papillomavirus infection in systemic lupus erythematosus women. Lupus 2017;26:944–51.
2. Li TH, Lai CC, Wang WH, Chen WS, Tsao TP, Tsai CY, et al. Risk of severe herpes simplex virus infection in systemic lupus erythematosus: analysis of epidemiology and risk factors analysis in Taiwan. Ann Rheum Dis 2019;78:941–6.
3. Dreyer L, Faurschou M, Mogensen M, Jacobsen S. High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: a long-term followup study in a Danish cohort. Arthritis Rheum 2011;63:3032–7.
4. Bernatsky S, Ramsey-Goldman R, Labrecque J, Joseph L, Boivin JF, Petri M, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun 2013;42:130–5.
5. Bae EH, Lim SY, Han KD, Jung JH, Choi HS, Kim CS, et al. Systemic lupus erythematosus is a risk factor for cancer: a nationwide population-based study in Korea. Lupus 2019;28:317–23.
6. Wang S, Chen Y, Xu X, Hu W, Shen H, Chen J. Prevalence of hepatitis B and hepatitis C virus infection in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Oncotarget 2017;8:102437–45.
7. Rojo-Contreras W, Olivas-Flores EM, Gamez-Nava JI, Montoya-Fuentes H, Trujillo-Hernandez B, Trujillo X, et al. Cervical human papillomavirus infection in Mexican women with systemic lupus erythematosus or rheumatoid arthritis. Lupus 2012;21:365–72.
8. Tam LS, Chan AY, Chan PK, Chang AR, Li EK. Increased prevalence of squamous intraepithelial lesions in systemic lupus erythematosus: association with human papillomavirus infection. Arthritis Rheum 2004;50:3619–25.
9. Wadstrom H, Arkema EV, Sjowall C, Askling J, Simard JF. Cervical neoplasia in systemic lupus erythematosus: a nationwide study. Rheumatology (Oxford) 2017;56:613–9.
10. Raposo A, Tani C, Costa J, Mosca M. Human papillomavirus infection and cervical lesions in rheumatic diseases: a systematic review. Acta Reumatol Port 2016;41:184–90.
11. Moscicki AB, Flowers L, Huchko MJ, Long ME, MacLaughlin KL, Murphy J, et al. Guidelines for cervical cancer screening in immunosuppressed women without HIV infection. J Low Genit Tract Dis 2019;23:87–101.
12. IBM Watson Health. IBM MarketScan Research Databases for Health Services Researchers (White Paper), 2019.
13. Watson M, Benard V, Flagg EW. Assessment of trends in cervical cancer screening rates using healthcare claims data: United States, 2003–2014. Prev Med Rep 2018;9:124–30.
14. Barnado A, Casey C, Carroll RJ, Wheless L, Denny JC, Crofford LJ. Developing electronic health record algorithms that accurately identify patients with systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2017;69:687–93.
15. Hwang JP, Ahmed S, Ariza-Heredia EJ, Duan Z, Zhao H, Schmeler KM, et al. Low rate of cervical cancer screening among women with hematologic malignancies after stem cell transplant. Biol Blood Marrow Transplant 2018;24:1094–8.
16. Deyo R, Cherkin D, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;3:613–9.
17. Tani C, Carli L, Mosca M, Baldini C, Consensi A, Doveri M, et al. Adherence to cervical cancer screening in an Italian SLE cohort [in Italian]. Reumatismo 2011;63:11–7.
18. Hall IJ, Tangka FK, Sabatino SA, Thompson TD, Graubard BI, Breen N. Patterns and trends in cancer screening in the United States. Prev Chronic Dis 2018;15:E97.
19. Silver MI, Kobrin S. Exacerbating disparities?: Cervical cancer screening and HPV vaccination. Prev Med 2020;130:105902.
20. MacLaughlin KL, Jacobson RM, Breitkopf CR, Wilson PM, Jacobson DJ, Fan C, et al. Trends over time in pap and pap-HPV cotesting for cervical cancer screening. J Womens Health (Larchmt) 2019;28:244–9.
21. Tam LS, Chan PK, Ho SC, Yu MY, Yim SF, Cheung TH, et al. Risk factors for squamous intraepithelial lesions in systemic lupus erythematosus: a prospective cohort study. Arthritis Care Res (Hoboken) 2011;63:269–76.
22. Klumb EM, Araujo ML Jr, Jesus GR, Santos DB, Oliviera AV, Albuquerque EM, et al. Is higher prevalence of cervical intraepithelial neoplasia in women with lupus due to immunosuppression? J Clin Rheumatol 2010;16:153–7.
23. Nath R, Mant C, Luxton J, Hughes G, Raju KS, Shepherd P, et al. High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. Arthritis Rheum 2007;57:619–25.
24. Feldman CH, Liu J, Feldman S, Solomon DH, Kim SC. Risk of high-grade cervical dysplasia and cervical cancer in women with systemic lupus erythematosus receiving immunosuppressive drugs. Lupus 2017;26:682–9.
25. Kavosi H, Javinani A, Kazemi-Rahmatabadi Z, Alyasin A, Sefidbakht S, Gharibdoost F, et al. Cervical cancer screening and Pap test non-adherence risk factors in systemic sclerosis patients. Eur J Cancer Prev 2020;29:266–9.

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BRIEF REPORT

Impact of the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus in a Multicenter Cohort Study of 133 Women With Undifferentiated Connective Tissue Disease

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Objective. We aimed to investigate the impact of applying the 2019 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) classification criteria for systemic lupus erythematosus (SLE) in a previously described cohort of women with undifferentiated connective tissue disease (UCTD).

Methods. This study included 133 women with UCTD. At the time of inclusion into the study, none of the patients met any classification criteria for other defined systemic connective tissue disease.

Results. When applying the 2019 EULAR/ACR classification criteria to the cohort, 22 patients (17%) fulfilled the classification criteria for SLE. Patients classified as having SLE had significantly higher frequencies of mucocutaneous manifestations (23% versus 5%; $P = 0.007$), arthritis (59% versus 17%; $P < 0.001$), isolated urine abnormalities (18% versus 1%; $P < 0.001$), and highly specific antibodies (50% versus 15%; $P < 0.001$) compared to the other patients with UCTD. At follow-up, these patients were statistically significantly more likely to also meet the 1997 ACR revised SLE criteria and the Systemic Lupus International Collaborating Clinics (SLICC) criteria (18.2% versus 1.8%; $P < 0.001$) compared to the other UCTD patients.

Patients who were diagnosed as having SLE according to the ACR 1997 update of the SLE revised criteria and the SLICC criteria during the follow-up scored higher on outcome measures when classified as having SLE according to the new 2019 EULAR/ACR classification criteria when compared to the other patients with UCTD (mean ± SD score 8.3 ± 3.7 versus 4.5 ± 4; $P < 0.05$).

Conclusion. When applying the 2019 EULAR/ACR criteria for SLE in a cohort of patients with UCTD, we observed that in up to 17% of cases the original classification could be challenged. New implementation will help to identify earlier patients at higher risk of developing more severe CTD manifestations.

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SIGNIFICANCE & INNOVATIONS

- When applying the new 2019 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) classification criteria for systemic lupus erythematosus (SLE), up to 17% of patients with undifferentiated connective tissue disease (UCTD) of our cohort of 133 patients met the classification criteria for SLE.
- Patients meeting the 2019 EULAR/ACR classification criteria for SLE had higher frequency of mucocutaneous manifestations, arthritis, isolated urine abnormalities, and highly specific antibodies to SLE.
- The present study supports the need for classification criteria for UCTD, especially to identify patients at higher risk of developing more severe CTD manifestations.

INTRODUCTION

Classification criteria for any given disease may provide some framework to help in diagnosis and are frequently used in this manner for teaching purposes. Such criteria traditionally have a high specificity, which generally is counterbalanced by a lower sensitivity. Consequently, few individuals are incorrectly labeled as having a disease (false positives), but a proportion of those with the disease diagnosis may be missed, i.e., labeled as not having the disease based on the classification criteria (false negatives). This may make classification criteria inappropriate for use in routine clinical care (1).

The case of undifferentiated connective tissue disease (UCTD) is emblematic. UCTD is an umbrella term describing a condition characterized by clinical and laboratory findings suggestive of connective tissue disease (CTD) but not fulfilling the current classification criteria for any definite CTD (2–4). In September 2019, a new set of classification criteria for systemic lupus erythematosus (SLE) was proposed (5). As a main difference from previous SLE classification criteria, the presence of antinuclear antibodies (ANA) was required as an entry criterion, showing a sensitivity of 96.1% and specificity of 93.4%. Several studies applied the new 2019 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) classification criteria for SLE to different cohorts and compared them with the previous classification criteria (6,7). However, it is unknown if the new classification criteria for SLE might impact the categorization of patients previously diagnosed with UCTD. Far from being only an academic question, the classification of having or not having SLE may pose clinical and logistic consequences, as patients with a diagnosis of SLE might be followed up according to a specific local protocol and have on-label access to certain medications (such as biologics) or may be eligible for participation in clinical trials. Herein, we applied the 2019 EULAR/ACR classification criteria for SLE (5) in a previously described cohort of 133 women with UCTD and ANA positivity (8).

PATIENTS AND METHODS

Our previous multicenter retrospective study (8) showed the fetal/perinatal and maternal outcomes of a cohort of UCTD patients who had ever been pregnant from 2010 to 2019. All patients were diagnosed with UCTD according to the established consensus (4,9,10) and were ANA positive. ANA positivity was confirmed and tested, as previously described (8). At the time of pregnancy, none of the patients fulfilled the 1997 ACR revised SLE criteria (11), the Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE (12), or any other defined systemic CTD.

Statistical analysis. Categorical variables were presented as number (%), and continuous variables were presented as mean ± SD. The significance of baseline differences was determined by chi-square test, Fisher's exact test, or the unpaired *t*-test, as appropriate. A 2-sided *P* value less than 0.05 was statistically significant. All statistical analyses were performed using SPSS, version 19.0.

RESULTS

Patient characteristics of the multicenter cohort. The analysis included 133 women (mean ± SD age at data collection 38.3 ± 6.8 years, mean ± SD disease duration at data collection 10.2 ± 5.1 years, and mean ± SD follow-up duration at data collection 9.2 ± 4.7 years). Clinical and laboratory characteristics of the cohort have been previously described (8). Briefly, the most common clinical manifestations were joint involvement (57.9%), followed by Raynaud's phenomenon (40.6%), photosensitivity (32.3%), and hematologic manifestations (27.1%). Thirty-three patients (24.8%) consistently tested positive for antiphospholipid antibodies (13), and 48 patients (36.1%) were also found to be positive for anti–extractable nuclear antigen, with anti-Ro/SSA positivity being the most common (45 patients [33.8%]).

Disease evolution at follow-up. Patients had a mean ± SD time of follow-up at data collection of 9.2 ± 4.7 years. During the follow-up, 16 patients (12%) developed novel clinical and/or laboratory features, and their diagnosis was changed to definite CTD. Mean time of follow-up before the diagnosis of definite CTD was achieved was 5.3 ± 2.8 years. Seven patients (5.3%) were later classified as having SLE according to the 1997 ACR revised SLE criteria (11) and the SLICC criteria for SLE (12), 7 patients (5.3%) were classified as having mixed CTD, 1 patient (0.75%) as having systemic sclerosis, and 1 patient as having Sjögren's syndrome.

Application of the 2019 EULAR/ACR classification criteria for SLE. When applying the 2019 EULAR/ACR classification criteria to the cohort, 22 patients (17%), at the time of their first pregnancy, scored ≥10 points and met the 2019 EULAR/ACR classification criteria of SLE (5). Table 1 and Figure 1 summarize the positive clinical and immunologic domains when considering

all the patients with UCTD and the patients who met the 2019 EULAR/ACR classification criteria for SLE at study entry.

When considering the most frequent positive domains, patients who scored ≥10 points (who, therefore, could have been classified at study entry as having SLE according to the 2019 EULAR/ACR classification criteria) had significantly higher frequency of mucocutaneous manifestations (23% versus 5%; $P = 0.007$), arthritis (59% versus 17%; $P < 0.001$), isolated urine abnormalities (isolated proteinuria ≥0.5 gm/24 hours [defined as presence of proteinuria without other urine abnormalities]; 18% versus 1%; $P < 0.001$), and highly specific antibodies (50% versus 15%; $P < 0.001$) when compared to patients with UCTD who scored <10 points.

Patients who met the 2019 EULAR/ACR SLE criteria at follow-up were statistically significantly more likely to be classified as having SLE according to the 1997 ACR revised SLE criteria (11) and SLICC criteria for SLE (12) compared to the other UCTD patients (18.2% versus 1.8%; $P < 0.001$), had fewer years of disease duration (8.23 versus 10.7; $P < 0.05$), and were more likely to develop preeclampsia in pregnancy (18% versus 0%; $P < 0.001$).

Patients who were diagnosed as having SLE according to the 1997 ACR revised SLE criteria and the SLICC criteria for SLE scored significantly higher when applying the 2019 EULAR/ACR classification criteria and as compared to the other UCTD patients (mean ± SD score 8.3 ± 3.7 versus 4.5 ± 4; $P < 0.05$). Table 2 summarizes the clinical and immunologic characteristic of

Table 1. Positive clinical and immunologic domains in patients*

	All (n = 133)	UCTD (n = 111)	SLE† (n = 22)	*P*
Mucocutaneous	11	6	5	0.007
Arthritis	32	19	13	<0.001
Serositis	7	4	3	0.054
Hematologic	25	21	4	0.94
Renal‡	5	1	4	<0.001
Antiphospholipid antibodies	28	26	2	0.131
Complement	21	16	5	0.954
Highly specific antibodies§	28	17	11	<0.001

* Values are the percentage unless indicated otherwise. SLE = systemic lupus erythematosus; UCTD = undifferentiated connective tissue disease.
† According to the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for SLE (ref. 5).
‡ Isolated proteinuria of ≥0.5 gm/24 hours without other urinary anomalies.
§ Including anti–double-stranded DNA and/or anti-Sm antibodies.

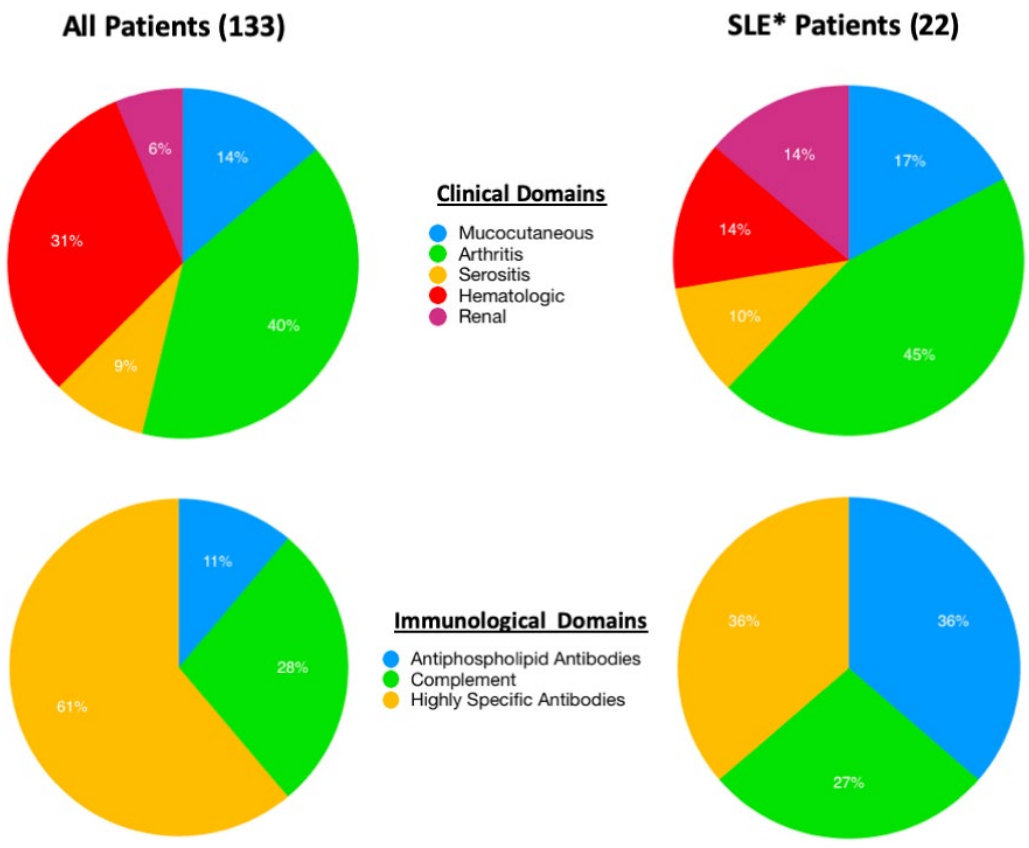

Figure 1. Positive clinical and immunological domains in all patients and in those with systemic lupus erythematosus (SLE). * = according to the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for SLE (ref. 5).

Table 2. Clinical and immunologic characteristics of patients who fulfilled the 1997 ACR revised SLE criteria and the SLICC criteria for SLE at follow-up*

	Clinical manifestations at study inclusion, prior SLE diagnosis	Clinical manifestations at follow-up, subsequent SLE diagnosis
Patient 1	Thrombocytopenia and arthritis	After 1 year, LN class IV and acute cutaneous lupus
Patient 2	Acute cutaneous lupus and arthritis	After 9 years, LN class IV
Patient 3	Low C3 and low C4 and arthritis	After 8 years, discoid lupus and anti-dsDNA positivity
Patient 4	Thrombocytopenia and anti-dsDNA positivity	After 5 years, arthritis and leucopenia
Patient 5	Antiphospholipid antibody positivity	After 3 years, LN class IV and anti-dsDNA positivity
Patient 6†	Isolated proteinuria and anti-dsDNA positivity	After 3 years, LN class IV and anti-dsDNA positivity
Patient 7	Arthritis	After 1 year, acute cutaneous lupus and hypo C3 and hypo C4

* Patients presented with new clinical manifestations and/or laboratory features and met the criteria after a mean ± SD follow-up duration of 4.3 ± 3.2 years. ACR = American College of Rheumatology; anti-dsDNA = anti–double-stranded DNA; LN = lupus nephritis; SLE = systemic lupus erythematosus; SLICC = Systemic Lupus International Collaborating Clinics.
† Isolated proteinuria of >0.5 gm/24 hours.

the patients who at the follow-up fulfilled the 1997 ACR revised SLE criteria and the SLICC criteria for SLE.

DISCUSSION

UCTD is a heterogeneous nosologic entity that includes various clinical scenarios, encompassing mild symptoms, such as arthralgia, to more severe manifestations, including severe organ involvement such as nonspecific interstitial pneumonia. Since the 1980s, many studies were carried out to analyze all the aspects of UCTD, from incidence, prevalence, clinical, and serologic profiles to possible evolution over time to a defined CTD. It is now fully accepted that UCTD represents a separate clinical entity and that only up to 30% of UCTD patients will develop a defined CTD in a 5-year time period (9,10). To date, UCTD has been reported as one of the most common rheumatic diseases (14); however, there are no validated classification criteria for patients with UCTD.

In our previous study, we demonstrated that, at follow-up, up to 12% of patients' disease evolved from UCTD to definite CTD (5.3% of patients toward SLE). These rates are in line with previous experiences reported in the current literature (15). When applying the 2019 EULAR/ACR classification criteria for SLE (5), up to 17% of patients would have been classified as having SLE before their pregnancy. This has some important implications, as, to date, there are no well-defined recommendations for the diagnosis and, more importantly, for the management of patients with UCTD. These patients with higher scores, according to the new 2019 EULAR/ACR classification criteria (5), had higher rates of preeclampsia during pregnancy, which suggests that they were at higher risk of pregnancy complications.

Considering the aforementioned findings, this study reveals some important messages. One could speculate that an early identification of SLE in patients with a previous diagnosis of UCTD might impact their clinical management, leading to a recommendation of a shorter duration of time to follow-up. Similarly, it might lead to an on-label access to specific treatment (e.g., belimumab), or eligibility to enter a clinical trial or to different forms of monetary reimbursement.

Finally, the lack of tailored classification criteria in UCTD might result in underestimating or neglecting patients who fall under the umbrella term of UCTD. For the patient, this may result in lack of timely follow-up and/or a lack of awareness and/or education of their underlying condition (as they are not classified as having a disease, per se), with an exhaustive list of possible consequences related to their nonclassification.

Some limitations of the present study should be acknowledged. First, the retrospective nature of the study could potentially affect the reproducibility of the results. Second, since this study carries an intrinsic sex bias, results might not be consistent when applied to a male population.

In conclusion, when applying the 2019 EULAR/ACR criteria for SLE in a cohort of women with UCTD, we observed that in up to 17% of cases the original classification could be challenged, advocating the need for updated classification criteria for UCTD. This study further supports the concept that in selected cases, classification and diagnostic criteria represent a continuum. When discriminating between conditions with a marked overlap, such as SLE and UCTD, the proposal of new classification criteria should balance specificity and sensitivity. When developing new classification criteria, one approach is to select patients and control groups who are as representative as possible of the settings (the medical practices) in which these criteria will be used.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Radin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Radin, Schreiber, Rubini, Foddai, Padovan, Cassarino, Franceschini, Andrade, Govoni, Marozio, Andreoli, Sciascia.
Acquisition of data. Cecchi, Bortoluzzi, Crisafulli, de Freitas, Bacco.
Analysis and interpretation of data. Benedetto, Bertero, Roccatello.

REFERENCES

1. Aggarwal R, Ringold S, Khanna D, Neogi T, Johnson SR, Miller A, et al. Distinctions between diagnostic and classification criteria? Arthritis Care Res (Hoboken) 2015;67:891–7.
2. LeRoy EC, Maricq HR, Kahaleh MB. Undifferentiated connective tissue syndromes. Arthritis Rheum 1980;23:341–3.
3. Alarcón GS, Williams GV, Singer JZ, Steen VD, Clegg DO, Paulus HE, et al. Early undifferentiated connective tissue disease. I. Early clinical manifestation in a large cohort of patients with undifferentiated connective tissue diseases compared with cohorts of well established connective tissue disease. J Rheumatol 1991;18:1332–9.
4. Doria A, Mosca M, Gambari PF, Bombardieri S. Defining unclassifiable connective tissue diseases: incomplete, undifferentiated, or both? J Rheumatol 2005;32:213–5.
5. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol 2019;71:1400–12.
6. Carneiro AC, Ruiz MM, Freitas S, Isenberg D. A comparison of three classification criteria sets for systemic lupus erythematosus: a study looking at links to outcome and mortality. Arthritis Care Res (Hoboken) 2020;72:1611–4.
7. Adamichou C, Nikolopoulos D, Genitsaridi I, Bortoluzzi A, Fanouriakis A, Papastefanakis E, et al. In an early SLE cohort the ACR-1997, SLICC-2012 and EULAR/ACR-2019 criteria classify non-overlapping groups of patients: use of all three criteria ensures optimal capture for clinical studies while their modification earlier classification and treatment. Ann Rheum Dis 2020;79:232–41.
8. Radin M, Schreiber K, Cecchi I, Bortoluzzi A, Crisafulli F, De Freitas C, et al. A multicentre study of 244 pregnancies in undifferentiated connective tissue disease: maternal/foetal outcomes and disease evolution. Rheumatology (Oxford) 2020;59:2412–8.
9. Mosca M, Tani C, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): a new frontier for rheumatology. Best Pract Res Clin Rheumatol 2007;21:1011–23.
10. Mosca M, Tani C, Neri C, Baldini C, Bombardieri S. Undifferentiated connective tissue diseases (UCTD). Autoimmun Rev 2006;6:1–4.
11. Hochberg MC, for the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
12. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.
13. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.
14. Bourn R, James JA. Preclinical lupus. Curr Opin Rheumatol 2015;27:433–9.
15. Bortoluzzi A, Furini F, Campanaro F, Govoni M. Application of SLICC classification criteria in undifferentiated connective tissue disease and evolution in systemic lupus erythematosus: analysis of a large monocentric cohort with a long-term follow-up. Lupus 2017;26:616–22.

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American College of Rheumatology
Empowering Rheumatology Professionals

BRIEF REPORT

Adaptation of American College of Rheumatology Rheumatoid Arthritis Disease Activity and Functional Status Measures for Telehealth Visits

Bryant R. England,[1] Claire E. H. Barber,[2] Martin Bergman,[3] Veena K. Ranganath,[4] Lisa G. Suter,[5] and Kaleb Michaud[6]

Objective. To provide guidance on the implementation of recommended American College of Rheumatology (ACR) rheumatoid arthritis (RA) disease activity and functional status assessment measures in telehealth settings.

Methods. An expert panel was assembled from the recently convened ACR RA disease activity and functional status measures working groups to summarize strategies for implementation of ACR-recommended RA disease activity (the Clinical Disease Activity Index [CDAI], Disease Activity Score in 28 joints using the erythrocyte sedimentation rate or the C-reactive protein level [DAS28-ESR/CRP], Patient Activity Scale II [PAS-II], Simplified Disease Activity Index [SDAI], and Routine Assessment of Patient Index Data 3 [RAPID3]) and functional status (the Health Assessment Questionnaire II [HAQ-II], Multidimensional Health Assessment Questionnaire [MDHAQ], and PROMIS physical function 10-item short form [PROMIS PF-10]) measures in telehealth settings.

Results. Measures composed of patient-reported items (disease activity: PAS-II, RAPID3; functional status: HAQ-II, MDHAQ, PROMIS PF-10) require minimal modification for use in telehealth settings. Measures requiring formal joint counts (the CDAI, DAS28-ESR/CRP, and SDAI) can be calculated using patient-reported swollen and tender joint counts. When the feasibility of laboratory testing is limited, the CDAI can be used in place of the SDAI, and scoring modifications of the DAS28-ESR/CRP without the acute-phase reactant are available. Assessment of the validity of these modifications is limited. Implementation of these measures can be facilitated by electronic health record collection, mobile applications, and provider/staff administration during telehealth visits.

Conclusion. The ACR-recommended RA disease activity and functional status measures can be adapted for use in telehealth settings to support high-quality clinical care. Research is needed to better understand how telehealth settings may impact the validity of these measures.

INTRODUCTION

The COVID-19 pandemic has increased the number of telehealth visits in rheumatology through telephone or videoconferencing in a synchronous or asynchronous manner. Many logistical challenges accompany the use of telehealth, including the regular assessment of rheumatoid arthritis (RA) disease activity and functional status that are central to RA management. The American College of Rheumatology (ACR) recently provided updated recommendations on RA disease activity measures and initial recommendations on functional status measures to support high-quality clinical care for routine clinical settings (1,2). This guidance has been used to inform quality measures on periodic assessment of disease activity and functional status assessment for providers who report through the Merit-Based Incentive Payment System (MIPS). To support the assessment of RA disease activity and functional status in telehealth settings, the ACR convened a working group to provide strategies for adopting the recommended

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SIGNIFICANCE & INNOVATIONS

- Due to the COVID-19 pandemic, telehealth has been widely adopted as a method to provide ongoing disease management for patients with rheumatoid arthritis (RA).
- The American College of Rheumatology recently provided an update on recommended RA disease activity and functional status for regular use to guide clinical care, with an emphasis on in-clinic visits. This report provides guidance for adapting these recommended measures for telehealth use.

RA disease activity and functional status measures for telehealth settings.

PATIENTS AND METHODS

The ACR convened an expert panel from the prior RA disease activity and functional status measures working groups (1,2). The recommended RA disease activity measures were the Clinical Disease Activity Index (CDAI), Disease Activity Score in 28 joints using the erythrocyte sedimentation rate or the C-reactive protein level (DAS28-ESR/CRP), Patient Activity Scale II (PAS-II), Simplified Disease Activity Index (SDAI), and Routine Assessment of Patient Index Data 3 (RAPID3), while the recommended functional status assessment measures were the Health Assessment Questionnaire II (HAQ-II), Multidimensional Health Assessment Questionnaire (MDHAQ), and PROMIS physical function 10-item short form (PROMIS PF-10). We evaluated the feasibility of implementation of the recommended functional status and disease activity measures and provided strategies for modification (if required) and use in telehealth settings to support patient care.

RESULTS

Modifying measures for telehealth settings. A summary of modifications needed for RA disease activity and functional status measures for telehealth use is provided in Table 1. The measures are recommended to be incorporated in routine practice with the same measures being utilized over time for a given patient and collection occurring at most visits. Minimal standards for reporting on disease activity and functional status are described in the ACR-endorsed performance measures used in the MIPS program (Table 1 footnote).

The 2019 ACR recommendations for disease activity and functional status included several entirely patient-reported measures that do not require substitution or modification of any components, thus retaining their original psychometric properties as summarized in the initial reports (1,2). These measures include the PAS-II and RAPID3 for RA disease activity and all recommended functional status assessment measures including the HAQ-II, MDHAQ, and PROMIS PF-10.

Measures requiring clinician assessments for tender and swollen joint counts and/or physician global scores are not feasible in their original operationalization in a telehealth setting but can be modified for use. The CDAI, DAS28-ESR/CRP, and SDAI all traditionally require provider-assessed swollen and tender joint counts. In place of provider joint counts, patient-reported joint counts may be substituted. While several studies have found moderate-to-strong correlations between patient and provider joint counts and patient and provider-derived composite disease activity scores (3–6), there are important caveats to the use of patient joint counts. First, most studies have incorporated baseline in-person training for conducting patient joint counts and found training to improve agreement with provider joint counts (6). Second, there is less agreement between patients and providers in the assessment of swollen joints compared to tender joint counts and for the assessment of smaller joints compared to larger joints (4–6). Finally, while group differences in RA disease activity scores using patient versus provider joint counts are typically small, there may be larger variability at the individual patient level. This individual variability may be related to disease activity level, RA disease duration, pain, disability, education level, health literacy, and language barriers (3–6). Provider global assessments included in the CDAI and SDAI may be collected as usual, although the authors recognize that the validity of the provider global assessment may be impacted by the use of telehealth.

Laboratory testing for the measurement of the ESR or CRP level is required for the DAS28-ESR/CRP and the SDAI. The feasibility of obtaining laboratory testing in conjunction with telehealth varies and may be problematic. Many patients are receiving disease-modifying antirheumatic drugs that require regular laboratory monitoring, and obtaining the ESR or CRP with this testing may be feasible. For others not receiving regular laboratory testing, those lacking access to a laboratory, or for those who consider the risk of SARS–CoV-2 exposure too great to obtain laboratory testing, the CDAI (calculated using patient-reported tender and swollen joint counts) could be used in place of the SDAI, and the DAS28-ESR/CRP may be scored without the acute-phase reactant but with an added patient pain visual analog scale (7). The DAS28 without acute-phase reactants has not undergone the same validation as the DAS28-ESR/CRP, and whether alternative disease activity state thresholds may improve agreement with the DAS28-ESR/CRP, such as those proposed for the DAS28-CRP, is unknown.

Collecting patient-reported measures and scoring via telehealth. While some measures, or components of measures, do not need modification, the processes for collecting the components of these measures, particularly patient-reported components, will change for many practices. The most significant factors for optimizing the collection of patient-reported measures

Table 1. Rheumatoid arthritis measures recommended by the American College of Rheumatology and telehealth modification summary*

	Abbreviated name	Components compatible with telehealth	Components needing modification for telehealth	Available modifications for telehealth
Disease activity†				
Clinical Disease Activity Index	CDAI	Patient global assessment; provider global assessment	Provider SJCs and TJCs	Replace provider SJCs and TJCs with patient-reported SJCs and TJCs
Disease Activity Score in 28 joints using the ESR or the CRP level	DAS28-ESR or DAS28-CRP	Patient global assessment	Provider SJCs and TJCs; laboratory testing‡	Replace provider SJCs and TJCs with patient-reported SJCs and TJCs; score DAS28 without acute-phase reactants§
Patient Activity Scale II	PAS-II	Patient global assessment; pain; HAQ-II	None	NA
Routine Assessment of Patient Index Data 3	RAPID3	Patient global assessment; pain; MDHAQ	None	NA
Simplified Disease Activity Index	SDAI	Patient global assessment provider global assessment	Provider SJCs and TJCs; laboratory testing‡	Replace provider SJCs and TJCs with patient-reported SJCs and TJCs; use CDAI in place of SDAI
Functional status¶				
Health Assessment Questionnaire II	HAQ-II	Patient questionnaire	None	NA
Multidimensional Health Assessment Questionnaire	MDHAQ	Patient questionnaire	None	NA
PROMIS physical function 10-item short form	PROMIS PF10	Patient questionnaire	None	NA

* ACR = American College of Rheumatology; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; GA = global assessment; NA = not applicable; PROMIS = Patient-Reported Outcomes Measurement Information System; RA = rheumatoid arthritis; SJC = swollen joint count; TJC = tender joint count.
† Percentage of patients age ≥18 years with a diagnosis of RA who have an assessment of disease activity using an ACR-preferred RA disease activity assessment tool at ≥50% of encounters for RA for each patient during the measurement year (https://qpp.cms.gov/docs/QPP_quality_measure_specifications/CQM-Measures/2020_Measure_177_MIPSCQM.pdf).
‡ Laboratory testing may be feasible for some patients and practices.
§ DAS28 without acute-phase reactants: $0.53 \times \sqrt{(28TJC)} + 0.31 \times \sqrt{(28SJC)} + 0.25 \times$ modified HAQ + 0.001 × Pain + 0.005 × Provider GA + 0.014 × Patient GA + 1.694.
¶ Percentage of patients age ≥18 years with a diagnosis of RA for whom a functional status assessment was performed at least once within 12 months (https://qpp.cms.gov/docs/QPP_quality_measure_specifications/CQM-Measures/2020_Measure_178_MIPSCQM.pdf).

are the technical capabilities of the patients, providers, and electronic medical record (EMR) vendors. In place of paper forms, patient-reported items can be completed by patients prior to their telehealth visit directly within some EMRs through a patient portal. In these situations, patients are provided a notification via email prior to their appointment to complete these measures, which are then reviewed during their medical appointment with their provider. Advantages of EMR-based measure collection are having minimal process changes for telehealth encounters and the integration of the measures into the medical record with the ability to track and trend measures over time. Disadvantages may include challenges in completing surveys for individuals with lack of computer access, limited computer literacy, and language barriers; additional support staff may be required for administration as well (8).

For health systems/clinics without patient portals capable of electronically capturing patient-reported measures from patients directly, providers or clinic staff may administer the surveys during the telehealth visit. The advantage of provider/staff administration during the visit is greater support for those with lower literacy in completion of the forms and likely higher provider understanding of the disease impact on patients through discussion of responses. The main disadvantages are the added time requirements to encounters for providers and/or added administrative/staff burden.

Last, measures can be obtained by mailings or electronic capture outside of the EMR. Mailed paper forms can be prefilled by the patient and recorded during the telehealth visit or mailed back to the provider. While this may lower the burden of provider/staff time during an encounter, this increases the possibility of lower response rates and requires administrative support for mailing and processing the measures. Smartphone and web-based apps can be used by the patient and/or the provider to collect these measures electronically during the telehealth visit or at regular intervals and summarized during the telehealth visit (8). Integration of mobile apps into health records is an active area of study (9). Scoring of RA disease activity and functional status measures can be facilitated by the ACR Clinical Practice Guidelines and Criteria App as well as on the ACR website (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Quality-Measurement/Disease-Activity-Functional-Status-Assessments) when not available within the EMR. A summary of strategies and potential barriers

Table 2. Strategies for telehealth implementation of rheumatoid arthritis (RA) disease activity and functional status measures by medium and potential barriers to implementation*

Medium	Collection strategies	Factors influencing feasibility and potential barriers†
EMR	Measures collected electronically by patient through patient portal before telehealth visit	Depends on EMR and EMR support on implementation and ability of patient to log on and complete
Smartphone or web-based application	Measures completed through smartphone or web-based application (e.g., ACR Clinical Practice Guidelines and Criteria App) and shared with provider	Depends on ability of patient to install and use app as well as transfer of data to clinical staff for recording in EMR
Video or telephone encounter	Provider collects measures from patient during synchronous telehealth encounter and records in EMR	Depends on the time available to providers/staff to collect these during the encounter and familiarity of patients with these measures
Mailed paper forms	Measures collected by patient at home on paper form and then mailed back or collected by clinical staff during telehealth visit	Depends on anticipated response rate, availability of administrative support staff to mail forms, and ability to complete the form in advance

* ACR = American College of Rheumatology; EMR = electronic medical record.
† For all collection strategies, patient health literacy and language should be considered. Time to collect, interpret, and report the results may vary depending on the medium used and clinic workflows.

for telehealth data collection is included in Table 2. While workflows vary between clinics and within clinics over time, successful collection of these measures can be facilitated by developing and assessing the performance of standard clinic workflows, educating staff and patients, and addressing patient health literacy and language barriers.

DISCUSSION

The current COVID-19 pandemic has heightened the need to care for patients with RA in an increasingly virtual environment. Following the announcement of the public health emergency, many rheumatology clinics were closed or had only limited face-to-face appointments due to social distancing restrictions and health system surge capacity planning. Therefore, it became necessary to deploy telehealth clinics using telephone or video-conference technology rapidly to ensure continuity of care. The routine collection and use of disease activity and functional status measures for high-quality RA care has been established as part of face-to-face encounters. While telehealth encounters have replaced face-to-face visits, the use of disease activity and functional status measures remain highly valuable for the management of RA during these uncertain times. Here, we have detailed approaches to facilitate the use of ACR-recommended RA disease activity and functional status measures in conjunction with telehealth encounters. All ACR-recommended RA disease activity (the CDAI, DAS28-ESR/CRP, PAS-II, RAPID-3, and SDAI) and functional status measures (the HAQ-II, MDHAQ, and PROMIS PF-10) can be adapted for use in telehealth settings using the provided modifications (Table 1).

These recommendations on modification of RA disease activity and functional status measures for telehealth settings were focused on measures recently recommended by the ACR because these measures were selected as those with the best validity and feasibility for routine use. Adapting these measures for telehealth clearly affects feasibility and, depending on the modifications needed to score these measures, may also affect the validity. Alterations to the validity of these measures is anticipated to be greatest for substituting patient-reported joint counts for provider joint counts (the CDAI, DAS28-ESR/CRP, and SDAI) and rescoring the DAS28 without acute-phase reactants. At a population level, these modifications appear to have little influence on the validity of these measures (3–5), although individual variation can be expected. Despite the content of patient-reported measures remaining unchanged, the heightened stress and anxiety experienced during the COVID-19 pandemic may similarly influence their validity (10). It is possible that other measures not initially selected as recommended disease activity and functional status measures may have a greater role for monitoring RA status in telehealth settings as a result of a lesser impact of telehealth modifications on their validity or their improved feasibility with telehealth. Research into the performance of RA disease activity and functional status measures in telehealth settings will be essential for identifying the most valid and feasible measures.

Given substantial variation between practices (e.g., EMR vendors, information technology [IT], administrative support), we were unable to directly compare the feasibility of different RA disease activity and functional status measures in the telehealth setting. Rather, we have provided suggestions for collecting these measures via different mediums. If the EMR is compatible with the collection of patient-reported measures directly, this offers the best potential for routine use. However, this approach requires IT infrastructure/support and patient technological capabilities. The US Health Information National Trends Survey found only 31% of the general public utilized patient portals in 2018, with female patients, White patients, and those with higher education levels more likely to use patient portals (11). If the EMR is not compatible or IT infrastructure is not available, changing

vendors or building this infrastructure will take substantial time, effort, and monetary commitment initially and for continued IT maintenance. The other methods of measure collection will require additional provider and/or administrator/clinical staff time. This may be compounded if provider joint counts are replaced with patient joint counts at the same telehealth encounter, necessitating patient education for the proper completion of these joint counts. Although most studies evaluating patient joint counts have utilized in-person training, patient resources and optimal training processes have not been established. The development of patient resources describing the conduct of patient joint counts as well as the process and importance of regularly monitoring disease activity and physical function should be a priority to facilitate virtual care. Furthermore, when initiating telehealth encounters, providers may already spend a significant amount of time in IT support (personally or with the patient) rather than providing direct care. A limitation of this work is that we did not conduct a new literature search on telehealth tools for the collection of disease activity or functional status measures, which was beyond the scope of this work.

Beyond the pandemic, the use of telehealth for RA care may be already happening in some areas due to geography, climate, transportation availability, and workforce shortages (12). It is likely that post-pandemic telehealth use will increase and help address rheumatology workforce challenges facing many regions (13). For example, telehealth may support safe remote monitoring of stable RA patients, allowing a redistribution of rheumatology resources to support urgent cases and new consultations. The virtual delivery of patient-reported outcomes has also been used to support treat-to-target initiatives in RA care and has been shown to be noninferior to routine care in the setting of a randomized controlled trial (14). Furthermore, electronic collection of patient-reported outcomes using EMRs or custom platforms or smartphone apps may support quality improvement and research initiatives. Virtual care complimented by electronic collection of patient-reported outcomes may also be acceptable and even preferred by some patients due to social and work obligations. For example, qualitative studies have shown that telehealth follow-up is acceptable to many patients with RA, although strategies may need to be developed to better assist some individuals requiring additional supports to adapt (15). Challenges exist in this environment, such as supporting patients and families with lower computer literacy and those for whom English is a second language. Additionally, it remains uncertain what is the optimal balance between telehealth and face-to-face encounters for long-term RA management.

In conclusion, the challenges of the pandemic have accelerated changes in the way we deliver care and have invited many opportunities to provide more patient-centered and flexible care. To support high-quality telehealth care for patients with RA in this new environment, we have described strategies for the modification and use of RA disease activity and functional status measures. Future research should continue to explore the validity of adapted disease activity and functional status measures for RA and develop strategies to support patients and physicians in virtual assessments of RA status.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Michaud had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. England, Michaud.

Analysis and interpretation of data. England, Barber, Bergman, Ranganath, Suter, Michaud.

REFERENCES

1. Barber CE, Zell J, Yazdany J, Davis AM, Cappelli L, Ehrlich-Jones L, et al. 2019 American College of Rheumatology recommended patient-reported functional status assessment measures in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2019;71:1531–9.
2. England BR, Tiong BK, Bergman MJ, Curtis JR, Kazi S, Mikuls TR, et al. 2019 update of the American College of Rheumatology recommended rheumatoid arthritis disease activity measures. Arthritis Care Res (Hoboken) 2019;71:1540–55.
3. Skougaard M, Bliddal H, Christensen R, Ellegaard K, Nielsen SM, Zavada J, et al. Patients with rheumatoid arthritis acquire sustainable skills for home monitoring: a prospective dual-country cohort study (ELECTOR clinical trial I). J Rheumatol 2020;47:658–67.
4. Riazzoli J, Nilsson JA, Teleman A, Petersson IF, Rantapaa-Dahlqvist S, Jacobsson LT, et al. Patient-reported 28 swollen and tender joint counts accurately represent RA disease activity and can be used to assess therapy responses at the group level. Rheumatology (Oxford) 2010;49:2098–103.
5. Radner H, Grisar J, Smolen JS, Stamm T, Aletaha D. Value of self-performed joint counts in rheumatoid arthritis patients near remission. Arthritis Res Ther 2012;14:R61.
6. Barton JL, Criswell LA, Kaiser R, Chen YH, Schillinger D. Systematic review and metaanalysis of patient self-report versus trained assessor joint counts in rheumatoid arthritis. J Rheumatol 2009;36:2635–41.
7. Bentley MJ, Greenberg JD, Reed GW. A modified rheumatoid arthritis disease activity score without acute-phase reactants (mDAS28) for epidemiological research. J Rheumatol 2010;37:1607–14.
8. Mollard E, Michaud K. Mobile apps for rheumatoid arthritis: opportunities and challenges. Rheum Dis Clin North Am 2019;45:197–209.
9. Austin L, Sharp CA, van der Veer SN, Machin M, Humphreys J, Mellor P, et al. Providing 'the bigger picture': benefits and feasibility of integrating remote monitoring from smartphones into the electronic health record. Rheumatology (Oxford) 2020;59:367–78.
10. Michaud K, Wipfler K, Shaw Y, Simon TA, Cornish A, England BR, et al. Experiences of patients with rheumatic diseases in the United States during early days of the COVID-19 pandemic. ACR Open Rheumatol 2020;2:335–43.
11. Hong YA, Jiang S, Liu PL. Use of patient portals of electronic health records remains low from 2014 to 2018: results from a national survey and policy implications. Am J Health Promot 2020;34:677–80.

12. Ferucci ED, Holck P, Day GM, Choromanski TL, Freeman SL. Factors associated with use of telemedicine for follow-up of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2020;72:1404–9.
13. Battafarano DF, Ditmyer M, Bolster MB, Fitzgerald JD, Deal C, Bass AR, et al. 2015 American College of Rheumatology Workforce Study: supply and demand projections of adult rheumatology workforce, 2015–2030. Arthritis Care Res (Hoboken) 2018;70:617–26.
14. De Thurah A, Stengaard-Pedersen K, Axelsen M, Fredberg U, Schougaard LM, Hjollund NH, et al. Tele-health followup strategy for tight control of disease activity in rheumatoid arthritis: results of a randomized controlled trial. Arthritis Care Res (Hoboken) 2018;70:353–60.
15. Knudsen LR, de Thurah A, Lomborg K. Experiences with telehealth followup in patients with rheumatoid arthritis: a qualitative interview study. Arthritis Care Res (Hoboken) 2018;70:1366–72.

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Do Obesity and Overweight Influence Disease Activity Measures in Axial Spondyloarthritis? A Systematic Review and Meta-Analysis

Augusta Ortolan, Mariagrazia Lorenzin, Mara Felicetti, and Roberta Ramonda

Objective. The aim of our systematic review and meta-analysis was to investigate whether overweight/obesity are associated with higher disease activity measures in patients with axial spondyloarthritis (SpA).

Methods. MEDLINE, PubMed, and Web of Science were searched using key terms corresponding to population (axial SpA patients), exposure (overweight/obesity), and outcome (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] and Ankylosing Spondylitis Disease Activity Score [ASDAS]). Predefined inclusion criteria were adult patients with axial SpA, exposure classified according to body mass index (BMI), BASDAI/ASDAS reported for each BMI group, and observational studies. The Newcastle-Ottawa Scale for cohort, cross-sectional, and case–control studies was used for quality check. Random-effects meta-analysis was used to pool results, which were expressed as the mean difference (MD) in BASDAI and ASDAS between BMI groups, with 95% confidence intervals (95% CIs).

Results. A total of 10 articles were included in the meta-analysis. The MD in BASDAI between normal BMI and overweight/obese patients was –0.38 (95% CI –0.56, –0.21; $P < 0.0001$); the MD in ASDAS between the same groups was –0.19 (95% CI –0.29, –0.09; $P < 0.0001$). The MD in BASDAI between normal BMI and overweight patients was –0.09 (95% CI –0.33, 0.15; $P = 0.45$), and the MD between normal BMI and obese patients was –0.78 (95% CI –1.07, –0.48; $P < 0.0001$). For ASDAS, the MD between normal BMI and overweight patients was –0.02 (95% CI –0.19, 0.15; $P = 0.79$), and the MD between normal BMI and obese patients was –0.42 (95% CI –0.60, –0.23; $P < 0.0001$).

Conclusion. Overweight and obese patients with axial SpA tend to present higher disease activity scores compared to patients with a normal BMI. This difference seems to be clinically meaningful only for the comparison between obese patients and patients with normal BMI, and more for BASDAI than ASDAS.

INTRODUCTION

Axial spondyloarthritis (SpA) is a chronic inflammatory disease mainly involving the axial skeleton (1). According to Assessment of SpondyloArthritis international Society (ASAS) criteria, 2 disease forms may be distinguished: radiographic axial SpA, formerly known as ankylosing spondylitis, and nonradiographic axial SpA (2). Despite differences in structural damage, the disease burden, in terms of disease activity, quality of life, and functional impairment, is similar between radiographic and nonradiographic axial SpA (3).

Disease activity in axial SpA is usually assessed via a 6-item questionnaire, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and a composite index called Ankylosing Spondylitis Disease Activity Score (ASDAS) (4,5). BASDAI was introduced first, but concerns were raised about the fact that it is an entirely patient-reported outcome, assigning equal weights to all items (6). In an effort to overcome these limitations, the ASDAS, a composite measure including patient-reported outcomes and inflammation indices, was developed in 2009 and has been used ever since (5,7). Regardless of the instrument, measuring disease activity over time in patients with axial SpA is paramount to assess clinical status and inform therapeutic decisions. However, physicians ought to be aware of conditions that might influence disease activity scores, such as obesity and overweight. Obesity is a frequent comorbid condition defined as a body mass index (BMI; the weight in kilograms divided by the square of the height in meters) of >30.0, while overweight is defined by a BMI between 25.0 and 29.9. Both conditions are associated with an increased all-cause mortality, though the relative risk is higher for obese than

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SIGNIFICANCE & INNOVATIONS

- Disease activity measures in axial spondyloarthritis can be influenced by body mass index (BMI).
- The effect of BMI is especially relevant on the Bath Ankylosing Spondylitis Disease Activity Index and when BMI is >30.
- The Ankylosing Spondylitis Disease Activity Score seems to be less affected by BMI.

overweight people (8). The mechanisms through which obesity or overweight could influence disease activity are manifold (9). First, adipose tissue produces many inflammatory mediators (adipokines), thus triggering or worsening a proinflammatory status in patients with axial SpA. Second, biomechanical factors such as abnormal loading, loss of trunk and lower-extremity muscle mass, and deregulated blood supply may increase joint pain. Finally, in obese patients an accelerated atherosclerosis of the abdominal aorta and of the lumbar arteries can be observed; this atherosclerosis causes disrupted perfusion of lumbar structures, potentially resulting in structural degeneration and low back pain (9).

While disease activity scores have been observed to decrease less with therapy in obese patients with axial SpA than in normal-weight patients (10,11), whether overweight or obesity per se may be a cause of higher disease activity scores is unclear. In other words, independently from changes related to a new treatment, whether obese patients in a steady state present with higher BASDAI or ASDAS scores is unknown. Therefore, the aim of our systematic review and meta-analysis was to investigate whether overweight and obesity (exposure) are associated with higher BASDAI and ASDAS scores (outcome) in adult patients with axial SpA (population).

MATERIALS AND METHODS

Literature search. A systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) was undertaken (12). MEDLINE, PubMed, and Web of Science were searched, without publication year restrictions. The last search update was on March 12, 2019.

The population of interest was considered to be adult patients (age ≥18 years) with radiographic axial SpA and nonradiographic axial SpA. Studies including patients with other rheumatic diagnoses were considered eligible only if the results for axial SpA were presented separately. The exposure was overweight and/or obesity as defined by a BMI of >25.0 and a BMI of >30.0, respectively (13), or for Asian populations a BMI of ≥23.0 and a BMI of ≥27.5 (14). The outcome of interest was disease activity as expressed by the BASDAI, a continuous score ranging from 0 to 10, or the ASDAS, a continuous score with 3 cutoffs at 1.3, 2.1, and 3.5, indicating inactive disease, low/high, and very high disease activity, respectively (4,15,16). Inclusion criteria were: 1) adult patients with axial SpA as defined by clinical diagnosis, European Spondylarthropathy Study Group criteria (17), ASAS criteria for axial SpA (2), or modified New York criteria for ankylosing spondylitis (18); 2) obesity and overweight defined according to the BMI categories described above; and 3) BASDAI and ASDAS scores as outcome of disease activity. Exclusion criteria were studies involving subjects with psoriatic arthritis as defined by Classification of Psoriatic Arthritis Study Group or Moll and Wright criteria (19,20), to obtain a homogeneous study population, and we excluded studies in languages other than English, Italian, or French. The types of studies considered for inclusion were observational cross-sectional studies, case–control studies, as well as baseline data of observational longitudinal studies. Notably, we did not find any randomized controlled trials and controlled clinical trials. Case series, case reports, editorials, and reviews were excluded.

We checked medial subject heading (MeSH) terms for axial SpA, obesity, overweight, BMI, BASDAI, and ASDAS to identify search terms in an attempt to capture all possible synonyms. In the final search, however, MeSH terms were not used, to avoid excluding more recent works. For the literature search, the concepts/terms "axial spondyloarthritis," "obesity/overweight," and "BASDAI/ASDAS" were combined. The actual terms used and their combination is more clearly described in Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24416/abstract.

Study selection, data extraction, and risk of bias assessment. Two reviewers (AO and ML) assessed each title and abstract on suitability for inclusion, according to the inclusion/exclusion criteria, followed by a full-text review if necessary. We gathered the following data from all included studies: main study design, characteristics of the study population (sex, age, and disease duration), exposure, and outcome measures. The quality of the extracted studies was then evaluated by the Newcastle-Ottawa Scale (NOS) for cross-sectional, cohort, and case–control studies (21). NOS study quality was graded according to the total score. Cross-sectional studies were graded as very good = 6–7, good = 5, satisfactory = 4, and unsatisfactory = 0–3. Cohort and case–control studies were graded as very good = 9–10, good = 7–8, satisfactory = 5–6, and unsatisfactory = 0–4 (22). A PRISMA flowchart was subsequently generated for the final selection of the studies to be included (see Results section for details).

Data analysis. We performed a meta-analysis on the studies that were deemed of at least satisfactory quality to provide a summary of the collected data. Since some studies subdivided BASDAI or ASDAS data into 2 BMI groups (normal versus overweight/obese), while others divided the data into 3 BMI groups (normal versus overweight versus obese), some data processing was necessary prior to meta-analysis. In particular, in the studies with 3 groups, the mean values of BASDAI or ASDAS scores in the overweight and obese groups were averaged using

a weighted mean to obtain BASDAI/ASDAS values for a single group ("overweight or obese"). A further calculation was needed to obtain BASDAI/ASDAS pooled SDs for the "overweight or obese" group, starting from separate SDs of obese and of overweight BMI categories (23).

Meta-analysis was then performed using the meta package in R, version 3.5.2. BASDAI and ASDAS estimates were reported as mean difference (MD) and SD between the patients with normal BMI and axial SpA and the overweight or obese patients. The statistical heterogeneity of meta-analysis was assessed using the I^2 statistic. Results were pooled using random-effects meta-analysis. Forrest plots were produced to represent effect sizes. In the studies where 3 BMI groups were presented, subanalyses were conducted to compare patients with normal BMI with axial SpA with overweight patients and obese patients separately.

RESULTS

Study selection. A total of 330 references were generated by the database search. After removing duplicates, the remaining 250 references were assessed for eligibility through first reading titles and abstracts. Of the 250 articles, 206 were further excluded during this process. The full-text of the remaining 44 articles was thus examined, leading to the exclusion of 33 articles that did not fulfill inclusion/exclusion criteria: 3 articles did not define the population according to predefined criteria, 8 articles defined exposure via different methods than BMI (e.g., visceral fat) or had a wrong exposure, 4 articles did not report the mean BASDAI or ASDAS score for each BMI group, 1 article was a review, and 17 other articles were duplicates (e.g., congress abstracts of the full study). The remaining 11 articles were considered for qualitative evaluation. The PRISMA flowchart of study selection is shown in Figure 1.

Study characteristics. The 11 studies included in the qualitative assessment were thoroughly examined to identify the type of publication (full text or conference abstract), design, number of participants, definition of population, exposure, and outcome (10,11,24–32). The results of data extraction are shown in Table 1. All articles were available as the full-text article except 1, which is in a conference abstract form. However, since that article contained adequate information to verify inclusion/exclusion criteria, we decided to keep it. The designs of the included studies were longitudinal (n = 3), cross-sectional (n = 7), and case–control study (n = 1). The definition of the populations was rather heterogeneous, because some studies applied some treatment-based or comorbidity-based exclusion criteria to patients with axial SpA (Table 1) (10,11,24,26,30).

The exposure was instead defined quite consistently according to the World Health Organization definition (14), although in some studies the comparison was made between 2 BMI groups

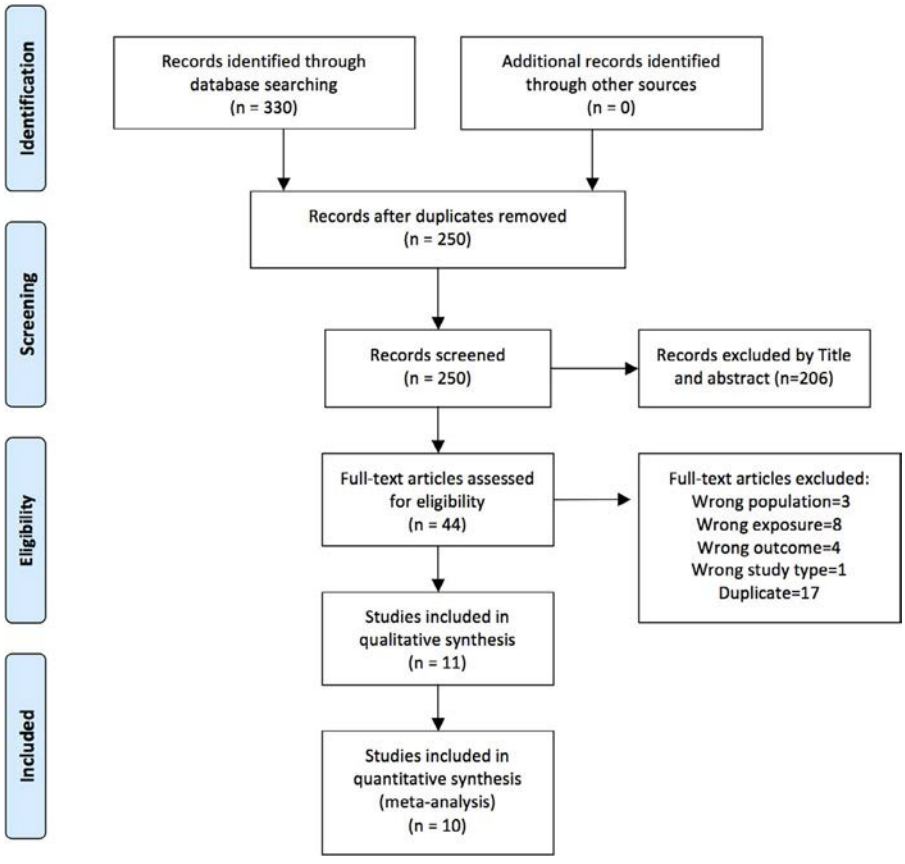

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study inclusions.

Table 1. Data extraction for studies included in the qualitative assessment*

Author, year (ref.)	Full article available	Design	Country	No. of pts	Population definition	% of r-ax SpA pts	Exclusion criteria (besides disease definition)	BMI categories	BASDAI for BMI	ASDAS for BMI
Al-Osami et al, 2018 (24)	Yes	Cross-sectional	Iran	170	mNY	100	Comorbidities (hypertension, diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, overlap, history of eye infection or trauma), recent DMARDs therapy or corticosteroids, elderly patients	1. Normal 2. Overweight 3. Obese	Yes	No
Durcan et al, 2012 (25)	Yes	Cross-sectional	Ireland	46	mNY	100	None	1. Normal 2. Overweight and obese	Yes	No
Hernandez-Breijo et al, 2019 (26)	Yes	Prospective cohort	Spain/ Netherlands	180	Clinical diagnosis and ASAS criteria for axial SpA	ND	None	1. Normal 2. Overweight and obese	Yes	Yes
Lee et al, 2017 (27)	Yes	Cross-sectional	China	194	ASAS criteria for axial SpA	74	None	1. Normal 2. Overweight and obese	Yes	No
Maas et al, 2016 (28)	Yes	Cross-sectional	Netherlands	461	ASAS criteria for axial SpA	90	None	1. Normal 2. Overweight 3. Obese	Yes	Yes
Micheroli et al, 2017 (10)	Yes	Prospective cohort	Switzerland	624	ASAS criteria for axial SpA	74	Fibromyalgia, underweight	1. Normal 2. Overweight 3. Obese	Yes	Yes
O'Shea et al, 2015 (29)	No	Cross-sectional	Ireland	267	Clinical diagnosis	100	None	1.Normal 2. Overweight 3. Obese	Yes	No
Ottaviani et al, 2012 (30)	Yes	Retrospective cohort	France	155	ESSG criteria	100	Inactive disease	1. Normal 2. Overweight 3. Obese	Yes	No
Rosas et al, 2017 (11)	Yes	Cross-sectional	Spain/Mexico	57	Clinical diagnosis	100	Patients not treated with adalimumab	1. Normal 2. Overweight 3. Obese	Yes	Yes
Rubio-Vargas et al, 2016 (31)	Yes	Cross-sectional	Netherlands	168	ASAS criteria for axial SpA	ND	None	1. Normal 2. Overweight and obese	Yes	Yes
Toy et al, 2017 (32)	Yes	Case–control	Turkey	28	mNY	100	Recent surgery related to the disease, additional systemic diseases, visual or cognitive problems	1. Normal 2. Overweight	Yes	No

* ASAS = Assessment of SpondyloArthritis international Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity; BMI = body mass index; DMARDs = disease-modifying antirheumatic drugs; ESSG = European Spondylarthropathy Study Group; mNY = modified New York criteria; ND = not determined; pts = patients; r-ax SpA = radiographic axial spondyloarthritis; ref. = reference.

(25,26,29,31) and in others among 3 groups (10,11,24,27,28,30). In the 1 case–control study, the comparison was only between normal and overweight patients, whereas obese patients were not included (32). All studies consistently presented the BASDAI mean value with SD and/or 95% confidence intervals (95% CIs). The same is true for ASDAS, except that ASDAS was only evaluated in 5 of 11 studies. Characteristics of the studies are shown in Table 1.

Risk of bias assessment. According to the NOS criteria for cohort studies, the 3 retrieved studies were of good quality. According to the NOS criteria for cross-sectional studies, 1 study was satisfactory, 2 were good, and 4 very good. The only case–control study was deemed unsatisfactory according to the NOS criteria for case–control studies, and thus it was not included in the meta-analysis (32). The main reason why cohort studies did not achieve the top scores was the lack of description on how BMI was calculated (e.g., self-reported weight and height). Reasons for lower scores in cross-sectional studies were the lack of description on how BMI was calculated, the sample size was often not justified, and the percentage of nonresponders was not always clearly indicated. The lone case–control study was deemed of poor quality mainly due to missing descriptions of case definition, representativeness of cases, and selection of controls. Table 2 reports details on how the single studies were graded.

Studies included in the meta-analysis. The main characteristics of the population of the 10 studies selected for the meta-analysis are shown in Table 3. The mean age ranged from 36.1 to 47.8 years. Disease duration ranged from 8.0 to 21.7 years across 9 studies. In 1 study, disease duration was not reported, though inclusion criteria included chronic back pain of recent onset (>3 months, <2 years) (31). Therefore, the disease duration in the latter study may have been much shorter than in the other studies. Male patients represented the vast majority of the population, except in the early axial SpA study, where the disease was almost evenly distributed between male and female patients (31). The prevalence of HLA–B27 was high, spanning 65% to 93% across 9 studies, with only 1 outlier, with a prevalence of 40% (24). Random-effects meta-analysis was applied owing to the observed clinical heterogeneity in the study population and the aforementioned issue of additional inclusion criteria in some of the studies.

As mentioned earlier, 4 studies reported 2 BMI groups and 6 studies reported 3. The first elaboration consisted of averaging the results of the overweight and obese group in each single study (weighted average and SD), thus obtaining a single group for "overweight or obese" patients. The mean value of BASDAI scores in the normal BMI group ranged from 2.8 to 6.0 across various studies, while in the overweight or obese group it ranged from 3.1 to 6.0. In all studies except 1, the BASDAI score of overweight or obese patients was higher than that observed in the normal BMI group (30). The mean value of ASDAS scores in the normal BMI groups ranged from 1.9 to 3.4, whereas in the overweight or obese group it ranged from 2.37 to 3.70. Results for the single studies are shown in Figures 2A (BASDAI) and 2B (ASDAS).

We conducted a meta-analysis to compare the pooled BASDAI and ASDAS scores of the normal BMI group with overweight or obese patients, by calculating MD and 95% CI (Figures 2A and 2B). According to the random-effects meta-analysis, patients with axial SpA with normal BMI were found to have a significantly lower BASDAI score versus the overweight or obese group (BASDAI MD –0.38 [95% CI –0.56, –0.21], $P < 0.0001$). For ASDAS, patients with normal BMI also had significantly lower disease activity scores than the overweight or obese group (ASDAS MD –0.19 [95% CI –0.29, –0.09], $P < 0.0001$). Heterogeneity statistics were apparently low across study estimates, albeit with a wide CI (I^2 = 0% [95% CI 0, 61.1] for BASDAI meta-analysis, I^2 = 0% [95% CI 0, 65.6] for ASDAS meta-analysis), suggesting measurements were consistent across studies.

Table 2. Application of Newcastle-Ottawa quality assessment scale for cohort, cross-sectional, and case–control studies*

Author, year (ref.)	Newcastle-Ottawa quality assessment scale score				
	Selection	Comparability	Outcome	Total score	Study quality
Cohort studies					
Hernandez-Breijo et al, 2019 (26)	4	1	2	7	Good
Micheroli et al, 2017 (10)	4	1	3	8	Good
Ottaviani et al, 2012 (30)	3	1	3	7	Good
Cross-sectional studies					
Al-Osami et al, 2018 (24)	2	1	1	4	Satisfactory
Durcan et al, 2012 (25)	1	1	3	5	Good
Lee et al, 2017 (27)	3	1	3	7	Very good
Maas et al, 2016 (28)	3	1	3	7	Very good
O'Shea et al, 2015 (29)	2	1	3	6	Very good
Rosas et al, 2017 (11)	1	1	3	5	Good
Rubio-Vargas et al, 2016 (31)	2	1	3	6	Very good
Case–control studies					
Toy et al, 2017 (32)	1	0	2	3	Unsatisfactory

* Values are the number of points ("stars") assigned according to the Newcastle-Ottawa quality assessment scale. ref. = reference.

Table 3. Characteristics of patients in studies included in the meta-analysis*

Author, year (ref.)	Age, mean ± SD years	Male, no. (%)	HLA–B27+, no. (%)	Disease duration, mean ± SD years	Normal BMI, no.	Obese and overweight, no.	Overweight (BMI ≥25 and <30), no.	Obese (BMI >30), no.	% treated with anti-TNF
Al-Osami et al, 2018 (24)	36.1 ± 9.0	158 (93)	68 (40)	8.3 ± 5.9	60	110	59	51	100
Durcan et al, 2012 (25)	45.1 ± 11.2	35 (76)	ND	12.9 ± 10.9	14	31	–	–	70
Hernandez-Breijo et al, 2019 (26)	47.0 ± 12.7	107 (59)	131 (73)	8.0 ± 5.9	78	102	–	–	0†
Lee et al, 2017 (27)	38.7 ± 13.7	150 (77)	159 (82)	7.1 ± 8.6	88	106	63	43	20
Maas et al, 2016 (28)	45.3 ± 12.8	303 (66)	361 (80)	17 ± 15.2	188	273	173	100	44
Micheroli et al, 2017 (10)	39.4 ± 11.6	388 (62)	487 (78)	13 ± 10.9	332	292	204	88	0†
O'Shea et al, 2015 (29)	47.8 ± ND	212 (79)	ND	21.7 ± ND	267	183	–	–	ND
Ottaviani et al, 2012 (30)	43.1 ± 12.4	98 (63)	96 (65)	8.0 ± 4.8	63	92	54	38	0†
Rosas et al, 2017 (11)	47.1 ± 10.4	37 (65)	44 (77)	9.8 ± 9.3	17	40	25	15	32
Rubio-Vargas et al, 2016 (31)	30.2 ± 8.2	81 (48)	156 (93)	ND	117	51	–	–	0

* BMI = body mass index; ND = not determined; ref. = reference; TNF = tumor necrosis factor.
† In cohort studies where a new therapy was started at baseline, we used baseline data (i.e. when patients were untreated) to compare disease activity between BMI categories.

Risk of bias across studies. To assess the risk of bias across studies, and small studies effect, a visual inspection of a funnel plot was performed (Figure 3). Considering the low number of included studies, the funnel plot had a rather symmetrical appearance, with an outlier corresponding to a small study with a large effect, likely to induce some degree of bias in the overall estimate (25). However, a linear regression test of funnel plot asymmetry yielded a nonsignificant result (t = –0.78, $P = 0.45$), allowing us to conclude an absence of major asymmetry.

Additional analysis. We performed additional meta-analyses in the 6 articles presenting BASDAI values for 3 BMI groups (normal/overweight/obese), to compare BASDAI scores between normal BMI versus overweight patients with axial SpA on one hand, and between normal BMI versus obese patients on the other hand (10,11,23,26,27,29). The MD in BASDAI between normal BMI and overweight patients with axial SpA was –0.09 (95% CI –0.33, 0.15; $P = 0.45$) (Figure 2C); MD in BASDAI values between normal BMI and obese patients was –0.78 (95% CI –1.07, –0.48; $P < 0.0001$) (Figure 2D). Heterogeneity statistics for the first and second comparison was not significant (respectively, $I^2 = 0$ [95% CI 0.0, 73.1], $P = 0.45$ and $I^2 = 0.0\%$ [95% CI 0.0, 0.0], $P = 0.95$).

For ASDAS, only 3 studies presented ASDAS values for the 3 BMI groups. The MD in ASDAS between normal BMI and overweight patients with axial SpA was –0.02 (95% CI –0.19, 0.15; $P = 0.79$); MD in ASDAS values between normal BMI and obese patients was –0.42 (95% CI –0.60, –0.23; $P < 0.0001$). Heterogeneity for the first and second comparison was not significant (respectively, $I^2 = 36.3\%$ [95% CI 0.0, 79.7], $P = 0.20$ and $I^2 = 20.4\%$ [95% CI 0.0, 91.7], $P = 0.28$).

Finally, we performed a comparison of disease activity indexes between overweight and obese patients with axial SpA. The MD in BASDAI between overweight and obese patients with axial SpA was –0.70 (95% CI –1.00, –0.40; $P < 0.0001$); heterogeneity was $I^2 = 0.0\%$ (95% CI 0.0, 43.3; $P = 0.81$. The MD in ASDAS between overweight and obese patients with axial SpA was –0.40 (95% CI –0.71, 0.08; $P = 0.013$); heterogeneity was $I^2 = 63.8\%$ (95% CI 0.0, 89.6; $P = 0.06$).

DISCUSSION

The current systematic review and meta-analysis highlighted the fact that, on average, there is a small but statistically significant difference (MD –0.38) in BASDAI scores between patients with axial SpA with a normal BMI and those with a pathologically increased BMI (overweight or obese). The same holds true for ASDAS scores (MD –0.19 between normal BMI and overweight/obese patients). According to the results of subanalyses, these differences in both BASDAI and ASDAS scores may be attributable mainly to the discrepancy between patients with normal BMI and obese patients with axial SpA. Instead, patients who are overweight do not have significantly different BASDAI and ASDAS scores compared to patients with normal BMI.

The consistency in our results is confirmed by the observation that throughout all included studies, mean BASDAI scores, as well as mean ASDAS scores, were always higher for abnormal BMI categories than for patients with normal BMI. Besides, the MD in BASDAI between patients with normal BMI and overweight/obese patients increased with BMI categories. This observation could hint at a plausible dose-effect relationship between fat mass, represented by BMI, and disease activity. However, the difference in BASDAI values was only statistically significant when comparing patients with normal BMI to obese patients, but not to overweight patients. Clinical significance seemed to be in accordance with the statistics; indeed, only a difference in BASDAI values of 0.78, (i.e., MD between normal BMI and obese patients), but not a difference in BASDAI of 0.09 (i.e., MD between normal BMI and overweight patients) is compatible with a clinically meaningful difference. In fact, although the smallest detectable change has not been precisely defined for BASDAI, literature describes the minimum clinically important improvement as equal to 0.7 (33). Therefore, the difference in BASDAI observed between patients with normal BMI and obese patients seems to be beyond measurement error.

In line with our results, some studies showed that the amount of visceral fat tissue appears to correlate well with disease activity in axial SpA in terms of BASDAI, and with less chances to reach a clinically important response both according to the BASDAI and ASDAS (34,35). Unfortunately, the scarcity of studies describing fat mass prevented the latter from being considered as an outcome in the current systematic literature review (34,35). Although BMI is admittedly not the most sensitive method to assess body adiposity, it certainly represents an easily available and widely accepted surrogate (36). Interestingly, BMI has also been shown to correlate with structural damage in axial SpA (37). This finding points toward the fact that inflammation might represent a mediator linking obesity and structural damage, and/or that biomechanical stress in obesity could enhance enthesophyte formation (37).

Despite the low number of studies where ASDAS was available, remarkably the ASDAS MD between normal BMI and obese or overweight patients tended to increase with increasing BMI category, similarly to BASDAI. These differences were, according to our meta-analysis, statistically significant except in the comparison between normal BMI and patients who were overweight only. However, the clinical significance of these finding is uncertain, because the smallest detectable change for ASDAS is described as ranging from 0.41 to 1.06, depending on the method (15). Thus, if indeed an ASDAS MD of –0.42 (i.e., MD between normal BMI and obese patients) could be beyond measurement error, a difference of –0.02 (i.e., MD between normal BMI and overweight patients) is certainly not.

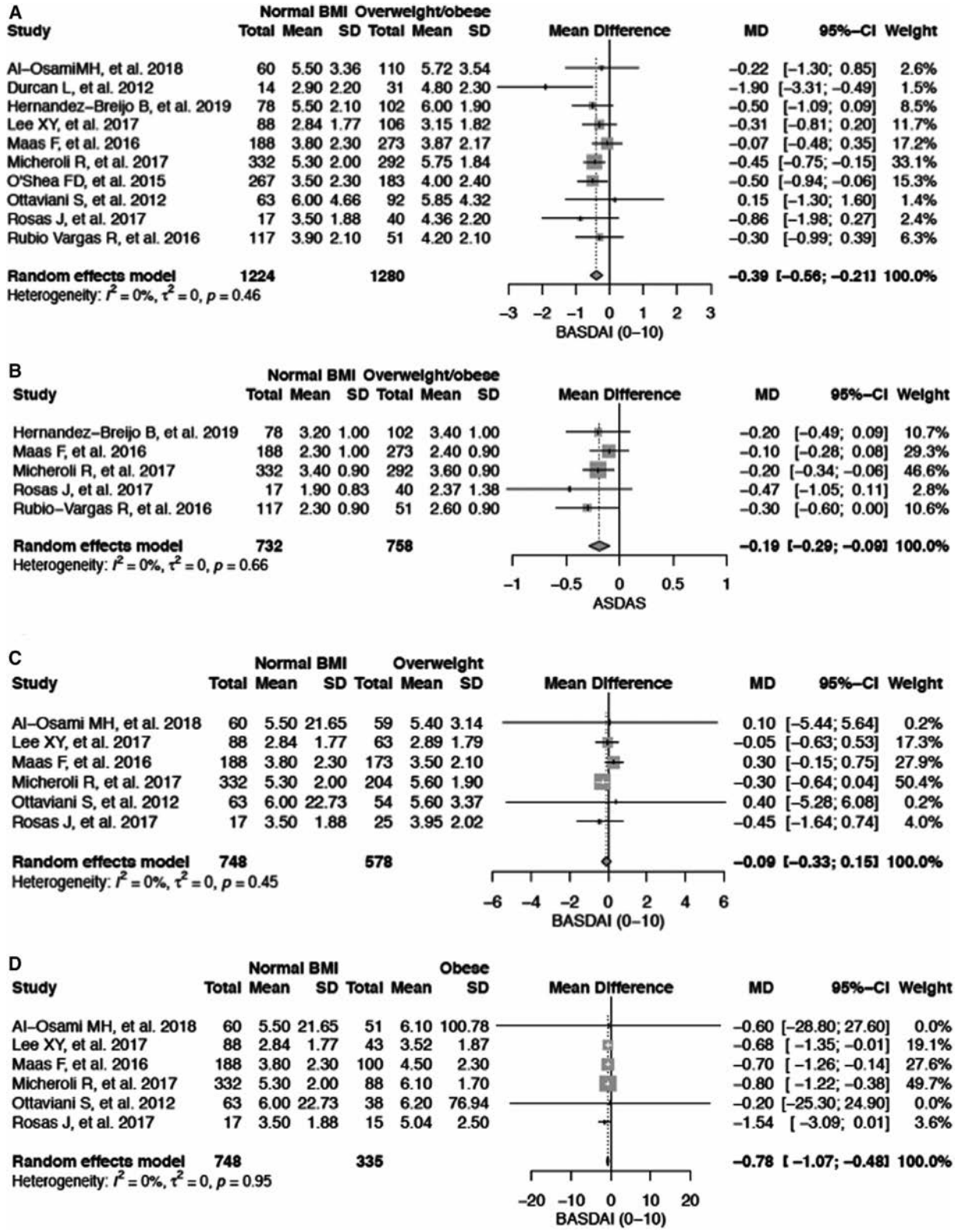

Figure 2. Random-effects meta-analysis. **A**, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in patients with normal body mass index (BMI) versus overweight or obese patients; **B**, Ankylosing Spondylitis Disease Activity Score (ASDAS) in patients with normal BMI versus overweight or obese patients; **C**, BASDAI in patients with normal BMI versus overweight patients only; **D**, BASDAI in patients with normal BMI versus obese patients only. 95%-CI = 95% confidence interval; MD = mean difference.

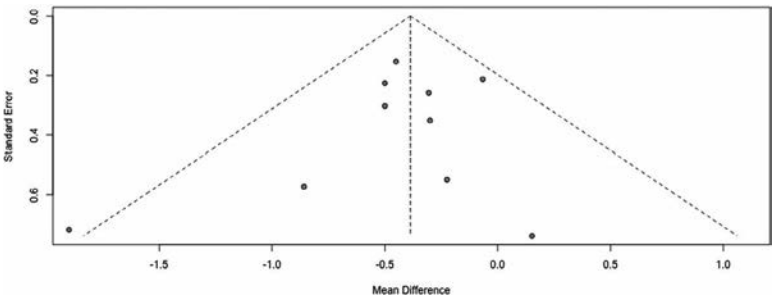

Figure 3. Funnel plot of studies included in the random-effects meta-analysis. Circles indicate each study.

Accordingly, a previous study included in our meta-analysis specifically examining the impact of BMI on disease activity showed that ASDAS does not seem to be affected by BMI (31). Since the ASDAS includes C-reactive protein level, it is supposed to best capture the inflammatory component compared to the BASDAI. Thus, the fact that the ASDAS does not show great differences according to BMI category might suggest that inflammation is only one of the mechanisms linking BMI to disease activity. In fact, obese patients with low back pain show higher patient-reported outcomes, which could explain why the BASDAI seems to be more impacted by BMI than the ASDAS (38).

For both the BASDAI and the ASDAS, the MD between overweight and obese patients was statistically significant and probably carried a clinical meaning. In fact, MD was 0.70 for BASDAI and 0.40 for ASDAS, with both values close to clinically important improvement/smallest detectable change. This observation seems to indicate that overweight patients with axial SpA are more similar to patients with normal BMI than to obese patients.

Regarding the characteristics of the included studies, we noticed the considerable heterogeneity in the pooled populations, due to various factors. First, some studies had a different primary outcome than the simple relationship between BMI and disease activity, such as drug response; therefore, additional inclusion/exclusion criteria concerning drug use were established in these studies. Second, some variation in disease definition, disease duration, HLA–B27 prevalence, and male to female ratio was present. On the other hand, statistical techniques seemed to highlight a very low grade of heterogeneity, albeit with a wide 95% CI, possibly in view of the very consistent definition of the exposure and outcome across studies. Overall, we decided to use a random-effects model to present more conservative results.

A substantial issue about exposure is that few of the included works defined how BMI was calculated (e.g., direct measurement or self-reported height and weight). Only 2 authors clearly stated that BMI had been obtained by direct measurement (27,28). While the BMI categories considered here were very broad, the possible disagreement between measurement methods may have been a source of misclassification (39). A further remark on exposure concerns underweight patients who were sometimes included in the "normal BMI" cohort, with prevalence between 1.7% and 3.3% (28,30,31). Given the very low prevalence of this condition, overall results are unlikely to have been severely biased by the inclusion of underweight patients.

The limitations of our study were the low number of studies available for the quantitative synthesis and the fact that we could only include observational studies, because no randomized controlled trial enrolling patients stratified by BMI was retrieved. Furthermore, the MD estimates obtained from original studies were rarely corrected or stratified according to confounding factors such as age and sex. In this regard, while some authors showed that the different BMI groups had similar mean age and sex distributions (11,25,31), others did not mention the distribution (10,24,26–28,30). We were able to mitigate such limitations via a strict methodology and consistency in the outcomes, thus allowing us to use MDs, instead of standardized MDs, as outcomes, which are much easier to interpret and can be directly related to the measurement unit of the outcome.

Our results offer one important observation: disease activity, especially when measured by the BASDAI, may be influenced by BMI. This finding mostly applies to truly obese patients and to a lesser extent to overweight patients. Our results are in line with previous reports highlighting a positive association between BMI and disease activity scores (25,27–29), and this meta-analysis has the further advantage of providing an effect size to this association. In other words, we defined to what extent disease activity measures can be influenced by obesity. Further studies are warranted to ascertain the potential impact of BMI on the ASDAS.

In conclusion, this systematic review found that disease activity scores of patients with normal BMI with axial SpA tend to be lower than the scores of overweight or obese patients. Notably, this difference appears to be relevant in clinical practice, especially when patients with normal BMI are compared to truly obese patients (BMI ≥30).

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ramonda had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ortolan, Ramonda.
Acquisition of data. Ortolan, Lorenzin.
Analysis and interpretation of data. Ortolan, Felicetti.

REFERENCES

1. Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. Arthritis Rheum 2006;54:569–78.
2. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777–83.
3. Erol K, Gok K, Cengiz G, Kilic G, Kilic E, Ozgocmen S. Extra-articular manifestations and burden of disease in patients with radiographic and non-radiographic axial spondyloarthritis. Acta Reumatol Port 2018;43:32–9.
4. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
5. Lukas C, Landewe R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18–24.ccc
6. Braun J, Kiltz U, Baraliakos X, van der Heijde D. Optimisation of rheumatology assessments: the actual situation in axial spondyloarthritis including ankylosing spondylitis. Clin Exp Rheumatol 2014;32:S-96–104.
7. Van der Heijde D, Lie E, Kvien TK, Sieper J, Van den Bosch F, Listing J, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:1811–8.
8. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 2006;355:763–78.
9. Wilson Zingg R, Kendall R. Obesity, vascular disease, and lumbar disk degeneration: associations of comorbidities in low back pain. PM R 2017;9:398–402.
10. Micheroli R, Hebeisen M, Wildi LM, Exer P, Tamborrini G, Bernhard J, et al. Impact of obesity on the response to tumor necrosis factor inhibitors in axial spondyloarthritis. Arthritis Res Ther 2017;19:164.
11. Rosas J, Llinares-Tello F, Senabre-Gallego JM, Barber-Valles X, Santos-Soler G, Salas-Heredia E, et al. Obesity decreases clinical efficacy and levels of adalimumab in patients with ankylosing spondylitis. Clin Exp Rheumatol 2017;35:145–8.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
13. World Health Organization. Obesity and overweight. 2019. URL: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight.
14. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.
15. Machado P, Landewe R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis 2011;70:47–53.
16. Machado PM, Landewe R, Heijde DV, Assessment of Spondylo-Arthritis international Society (ASAS). Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. Ann Rheum Dis 2018;77:1539–40.
17. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991;34:1218–27.
18. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.
19. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.
20. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55–78.
21. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
22. Lodge CJ, Tan DJ, Lau MX, Dai X, Tham R, Lowe AJ, et al. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. Acta Paediatr 2015;104:38–53.
23. Hedges LV, Olkin I. Statistical methods for meta-analysis. Dan Diego: Academic Press; 1985. p. 79.
24. Al-Osami MH, Hameed EK, Al-Hamadani AM. Effect of HLA-B27 status and body mass index on the clinical response to infliximab in ankylosing spondylitis patients. Indian J Rheumatol 2018;13:33–7.
25. Durcan L, Wilson F, Conway R, Cunnane G, O'Shea FD. Increased body mass index in ankylosing spondylitis is associated with greater burden of symptoms and poor perceptions of the benefits of exercise. J Rheumatol 2012;39:2310–4.
26. Hernandez-Breijo B, Plasencia-Rodriguez C, Navarro-Compan V, Martinez-Feito A, Jochems A, Kneepkens EL, et al. Association between concomitant csDMARDs and clinical response to TNF inhibitors in overweight patients with axial spondyloarthritis. Arthritis Res Ther 2019;21.
27. Lee YX, Kwan YH, Png WY, Lim KK, Tan CS, Lui NL, et al. Association of obesity with patient-reported outcomes in patients with axial spondyloarthritis: a cross-sectional study in an urban Asian population. Clin Rheumatol 2017;36:2365–70.
28. Maas F, Arends S, van der Veer E, Wink F, Efde M, Bootsma H, et al. Obesity is common in axial spondyloarthritis and is associated with poor clinical outcome. J Rheumatol 2016;43:383–7.
29. O'Shea FD, Gallagher P, Sullivan C, Sheehy C, Silke C, O'Rourke K, et al. High body mass index in ankylosing spondylitis is associated with greater disease activity and more functional impairment. Ann Rheum Dis 2015;74:500–1.
30. Ottaviani S, Allanore Y, Tubach F, Forien M, Gardette A, Pasquet B, et al. Body mass index influences the response to infliximab in ankylosing spondylitis. Arthritis Res Ther 2012;14:R115.
31. Rubio Vargas R, van den Berg R, van Lunteren M, Ez-Zaitouni Z, Bakker PA, Dagfinrud H, et al. Does body mass index (BMI) influence the Ankylosing Spondylitis Disease Activity Score in axial spondyloarthritis? Data from the SPACE cohort. RMD Open 2016;2:e000283.
32. Toy S, Ozbag D, Altay Z. The effects of pre-obesity on quality of life, disease activity, and functional status in patients with ankylosing spondylitis. North Clin Istanb 2017;4:52–9.
33. Kviatkovsky MJ, Ramiro S, Landewe R, Dougados M, Tubach F, Bellamy N, et al. The minimum clinically important improvement and patient-acceptable symptom state in the BASDAI and BASFI for patients with ankylosing spondylitis. J Rheumatol 2016;43:1680–6.

34. Aydin M, Aydin F, Yuksel M, Yildiz A, Polat N, Akil MA, et al. Visceral fat reflects disease activity in patients with ankylosing spondylitis. Clin Invest Med 2014;37:E186–90.
35. Vodnizza SE, Nurmohamed MT, Visman IM, van Denderen JC, Lems WF, Jaime F, et al. Fat mass lowers the response to tumor necrosis factor-alpha blockers in patients with ankylosing spondylitis. J Rheumatol 2017;44:1355–61.
36. Okorodudu DO, Jumean MF, Montori VM, Romero-Corral A, Somers VK, Erwin PJ, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. Int J Obes (Lond) 2010;34:791–9.
37. Bakirci S, Dabague J, Eder L, McGonagle D, Aydin SZ. The role of obesity on inflammation and damage in spondyloarthritis: a systematic literature review on body mass index and imaging. Clin Exp Rheumatol 2020;38:144–8.
38. Vincent HK, Seay AN, Montero C, Conrad BP, Hurley RW, Vincent KR. Functional pain severity and mobility in overweight older men and women with chronic low-back pain: part I. Am J Phys Med Rehabil 2013;92:430–8.
39. Elgar FJ, Stewart JM. Validity of self-report screening for overweight and obesity: evidence from the Canadian Community Health Survey. Can J Public Health 2008;99:423–7.

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Patient-Reported Impact of Axial Spondyloarthritis on Working Life: Results From the European Map of Axial Spondyloarthritis Survey

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Objective. To evaluate work-related issues (WRIs) and their determinants in patients with axial spondyloarthritis (SpA) across Europe.

Methods. The European Map of Axial Spondyloarthritis is a cross-sectional online survey (2017–2018) of unselected patients with self-reported axial SpA from 13 European countries. Participants were classified as active or inactive members of the labor force according to the International Labor Organization standards. Those employed reported WRIs due to axial SpA in the past 12 months. Sociodemographic characteristics and patient-reported outcomes were compared between patients with and without WRIs. Stepwise regression analysis was conducted to identify independent determinants of WRIs.

Results. The sample comprised 2,846 patients with axial SpA, 1,653 were active members of the labor force, 1,450 were employed, and of those employed, 67.7% reported at least 1 WRI. The most frequently reported WRIs were taking sick leave (56.3%), difficulty fulfilling working hours (44.6%), and missing work for doctor's appointments (34.6%). Of the total sample, 74.1% declared that they had faced or would face difficulties finding a job due to axial SpA. Patients with WRIs were more often female, were less likely to be married or in a relationship, and had a higher educational level, poorer patient-reported outcomes, and a greater prevalence of anxiety and depression. Multivariable regression showed that WRIs were associated with a higher Bath Ankylosing Spondylitis Disease Activity Index score (odds ratio [OR] 1.30 [95% confidence interval (95% CI) 1.16–1.45]) and the 12-item General Health Questionnaire score (OR 1.15 [95% CI 1.09–1.22]), and were negatively associated with inflammatory bowel disease (OR 0.58 [95% CI 0.36–0.91]).

Conclusion. Approximately two-thirds of employed patients experienced WRIs due to axial SpA. Association between disease activity and psychological distress with WRIs suggests the need to ensure that axial SpA patients receive the required support to cope with their working life.

INTRODUCTION

Axial spondyloarthritis (SpA) is a chronic inflammatory disease usually affecting the axial skeleton, including the sacroiliac and spinal joints. Currently, axial SpA comprises patients with nonradiographic axial SpA and radiographic axial SpA, also known as ankylosing spondylitis (1).

Axial SpA has a great impact on working life, a key sphere within overall quality of life. Previous studies have shown that persistent patterns of high disease activity among axial SpA patients are

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SIGNIFICANCE & INNOVATIONS

- This study presents data on a large sample of patients with axial spondyloarthritis (SpA) from 13 European countries, reducing territorial and cultural biases present in other published studies.
- Traditionally, studies on rheumatic diseases have focused on the medical or clinical parameters, while this study focuses on patient-reported outcomes, contributing to the growing interest in the scientific literature for the patient's perspective.
- To provide reliable and robust data on unemployment, we calculated the unemployment rate following the International Labor Organization standards on active and inactive populations, to compare the rate of unemployment in the countries to that of their respective general populations.
- Additionally, to the best of our knowledge, this is the first study to report reliable unemployment rates of axial SpA patients of a group of countries that are not frequently the focus of research.

associated with loss of work productivity (2) and increased probability of work disability (3). Patients with axial SpA are also known to experience significant career development limitations as a result of their condition (4). Experiencing problems at work also predicts poor out-of-work functioning and psychological issues (5,6). Certain psychosocial factors such as social deprivation, depression, anxiety, and reduced self-efficacy are associated with increased presenteeism and absenteeism (7), thereby highlighting the bidirectional relationship between workplace and psychosocial functioning.

Access to health care is essential to avoid a progressive worsening of functional, work, and psychological and social health and the attendant consequences for the individual, society, and the economy. This fact is supported by the Assessment of SpondyloArthritis international Society/European Alliance of Associations for Rheumatology, which expressly recommend that work productivity loss should be taken into account when assessing the cost-effectiveness of treatments (8).

Interactions between disease activity, psychosocial factors, and disruption of patients' working lives stimulate the focus on the development of comprehensive and holistic management for axial SpA (9). Consequently, evaluating the working life of patients with axial SpA in all respects is important: employment status, unemployment rates, and work-related issues (WRIs), as well as the association of these problems with sociodemographic characteristics of patients and their patient-reported outcomes. Unfortunately, methodologic differences when defining the employment ratio in different studies has led to inconsistent conclusions, often within the same population (7,10,11).

One of the objectives of the European Map of Axial Spondyloarthritis (EMAS) is to provide reliable and standard indicators, collected using the same methodology, on all aspects related to the lives of patients living with axial SpA, and further, to allow comparisons between countries across Europe (12). The aim of the present analysis was to assess the working life of patients with axial SpA, including WRIs and their determinants in Europe.

MATERIALS AND METHODS

The EMAS project is promoted by the Axial Spondyloarthritis International Federation and by the Spanish Federation of Spondyloarthritis Associations (CEADE). The project is led by the Health and Territory Research group of the University of Seville and a steering committee composed of patient representatives and internationally recognized rheumatologists and psychologists specialized in axial SpA.

Design and survey development. EMAS was an observational, cross-sectional online survey of unselected patients self-reporting as having axial SpA from Austria, Belgium, France, Germany, Italy, The Netherlands, Norway, Russia, Slovenia, Sweden, Switzerland, and the UK. The questionnaire was adapted from the Spanish Atlas of Axial Spondyloarthritis 2017 (13), a patient survey held from January to March 2016, promoted by Health and Territory Research and CEADE with the support of the Max Weber Institute and Novartis Farmacéutica Spain. Data from the Atlas of Axial Spondyloarthritis in Spain 2017 (14) were retrospectively added to the EMAS database.

The EMAS patient questionnaire included 108 items related to 12 different areas: sociodemographic and anthropometric characteristics, disability assessment, work life, daily life, lifestyle habits, diagnostic journey, health care resource utilization, treatment, comorbidities (including extraarticular manifestations), psychological health, disease outcomes, and patient disease-related attitudes. The EMAS questionnaire was originally developed in Spanish and subsequently translated into English, followed by Dutch, French, German, Italian, Russian, Swedish, and Slovenian. Prior to the start of data collection, participating countries were asked to assess and modify questions for local relevance, with guidance to only make essential changes in order to maintain consistency on an international level.

Sample selection and recruitment. Detailed information on the design and procedures of the EMAS study can be found elsewhere (12). Briefly, European patients with a self-reported clinician-provided diagnosis of axial SpA (radiographic or nonradiographic), age ≥18 years, who had visited a health care professional for axial SpA in the 12 months prior to participation were included in the survey.

Participants were recruited between July 2017 and March 2018 by the global research agency Ipsos SA, formerly GfK, through their existing online panel. In Austria, France, Spain, Norway, Slovenia, Sweden, The Netherlands, Italy, Russia, and Switzerland, patient organizations also supported recruitment by distributing the survey to their associated members (Figure 1). All patients agreed to their participation through informed consent

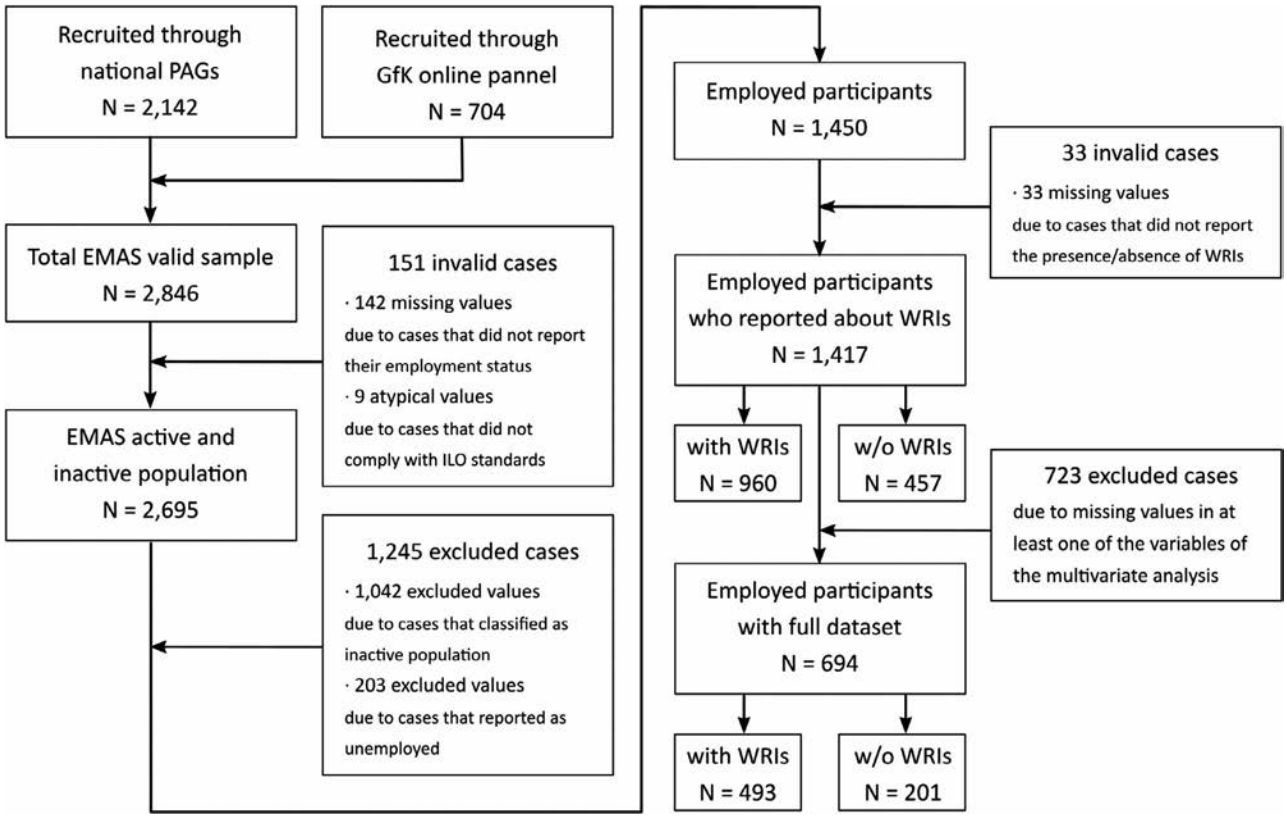

Figure 1. European Map of Axial Spondyloarthritis (EMAS) flow diagram of patient recruitment and selection. ILO = International Labor Organization; PAGs = patient advocacy groups; w/o = without; WRIs = work-related issues.

and were asked to provide explicit opt-in consent prior to participating in the EMAS survey. Participant data were anonymized.

Labor force and employment rates. Participants were asked about their employment status through a multiple-choice question in which they could choose 1 option from the following: employed, unemployed, on temporary sick leave, on permanent sick leave, retired, early retirement, student, or homemaker. Using this information, patients were classified as part of the labor force (active population) or the economically inactive population according to the International Labor Organization standards (15,16). Those considered active, or in the labor force, included the employed and unemployed of working age (15–64 years). Participants who reported being on temporary sick leave, permanent sick leave, retired, having taken early retirement, or being a student or homemaker were considered part of the inactive population. Figure 1 shows the sample selection process for the study data analysis. Employment and unemployment rates were calculated comparing employed and unemployed participants within the labor force.

Impact on working life. Those in employment were also asked to report WRIs due to axial SpA in the 12 months prior to participating in the EMAS survey via a yes/no question. Those reporting "yes" were asked to choose the WRIs applicable to them from the following list: 1) I asked for some days off/leave of absence, 2) I took sick leave, 3) I reduced my working hours, 4) I missed work only for the time my doctor's appointment took, 5) It has been difficult for me to fulfill working hours, 6) I have occasionally changed my work shift, 7) My professional life has suffered (e.g., missed promotion), or 8) I had to give up my previous job.

Furthermore, all participants were asked the following yes/no questions: 1) Do you think it is or would be difficult for you to find a job because of your spondylitis/spondyloarthritis? 2) Do you think your current or past work choice was in any way determined by your spondylitis/spondyloarthritis?

Other patient-reported outcomes. In addition, the following patient-reported outcomes were also collected in the EMAS questionnaire (12).

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The BASDAI is a validated self-administered questionnaire assessing disease activity in patients with axial SpA, capturing symptoms of fatigue, spinal pain, peripheral arthritis, enthesitis, and the intensity and duration of morning stiffness. Possible scores range from 0 (no activity) to 10 (maximum activity) (17).

Spinal Stiffness Index. This index assesses the self-reported degree of stiffness experienced by patients in the spinal column, distinguishing between the cervical, dorsal, and lumbar areas. The index is the result of adding an unweighted degree of stiffness in these 3 spinal regions on a scale of lesser to greater effect (from 3 to 12): where a value of 3 would imply no stiffness, 4–6 mild stiffness, 7–9 moderate stiffness, and 10–12 significant stiffness. This index showed an acceptable internal reliability (Cronbach's α = 0.79) (13).

Functional Limitation Index. This index, developed specifically for this study, assesses the degree of functional limitation in 18 daily life activities (dressing, bathing, showering, tying shoe laces, moving about the house, climbing stairs, getting out of bed, using the bathroom, shopping, preparing meals, eating, household tasks, walking down the street, using public transportation, driving, going to the doctor, doing physical exercise, and having intimate relations). The score is generated by adding the nonweighted degree of functional limitation of all activities, using a score of 0–3 (0 = no limitation, 1 = low limitation, 2 = medium limitation, and 3 = high limitation), with a total result between 0 and 54. Thus, a functional limitation value of 0–18 would imply low limitation, 18–36 medium limitation, and 36–54 high limitation. Cronbach's α = 0.97, demonstrating excellent internal reliability (13).

12-item General Health Questionnaire (GHQ-12). This questionnaire measures psychological distress, using 12 items (18), which are then transformed into a dichotomous score (0-0-1-1) called the GHQ-12 score. The cutoff point of 3 implies those experiencing a risk of psychological distress (19).

Statistical analysis. The sociodemographic variables included in this analysis were age, sex, educational level, marital status, and income level and patient-reported outcomes including the BASDAI, spinal stiffness and functional limitation, the presence of both physical and psychological comorbidities, extraarticular manifestations such as uveitis and inflammatory bowel disease (IBD), and psychological distress as measured by the GHQ-12.

The distribution of all variables was compared between patients with and without WRIs using Mann-Whitney and chi-square tests (for scale and categorical variables, respectively). A univariate logistic regression was carried out to explain the presence of the WRIs individually for each variable (including sociodemographic characteristics, patient-reported outcomes, and psychological health). To identify independent determinants of WRIs, a multivariate stepwise regression analysis with candidate variables that showed an association with the WRIs in the univariate analysis was conducted.

RESULTS

Labor force. There were 2,846 participants in the EMAS survey, of which 2,704 reported their employment status. Nine patients were excluded from the analysis (making a total of 2,695) because they reported being employed or unemployed and age >65 years and therefore could not be considered as either part of the labor force or the inactive population following International Labor Organization classification. Of the selected sample, 1,653 (61.3%) were part of the labor force, while 1,042 (38.7%) were economically inactive. Among those inactive, 29.2% were on temporary sick leave, 28.0% on permanent sick leave, 22.1% retired, 10.9% homemakers, 5.7% students, and 4.1% on early retirement (Table 1). Approximately 90% of participants with axial SpA on sick leave, either temporary or permanent, declared that their condition was the cause of their employment status. Two-thirds of early retired participants reported axial SpA as the cause for their retirement. Within the labor force, 1,450 (87.7%) were employed, and 203 (12.3%) unemployed.

A total 65.3% of participants with axial SpA who were unemployed reported that the disease had been the main cause of their unemployment, compared to 34.7% who reported that it had not influenced their joblessness. Notably, unemployment rates across axial SpA patients in the labor force (n = 1,653) varied greatly between the different EMAS participating countries, ranging from 0.4% in Norway to 21.7% in Spain, with average values nearing 11.8%, as in France (Figure 2).

WRI-related issues and their determinants. Of all participants who were either part of the labor force (active population) or the inactive population (n = 2,695), 1,967 reported whether they had faced or would face difficulties finding a job due to axial SpA (1,457 [74.1%] declared "yes"). Additionally, participants were asked whether their present or past work choice was determined

Table 1. Employment status of participants in the labor force and economically inactive population (n = 2,695)*

Population, employment status	No. (%)
Active population (n = 1,653 [61.3%])	
Employed	1,450 (87.7)
Unemployed	203 (12.3)
Total	1,653 (100.0)
Inactive population (n = 1,042 [38.7%])	
Temporary sick leave	304 (29.2)
Permanent sick leave	292 (28.0)
Retired	230 (22.1)
Homemaker	114 (10.9)
Student	59 (5.7)
Early retirement	43 (4.1)
Total	1,042 (100.0)

* Based on International Labor Organization criteria, which define the active population or labor force as the sum of persons ages 15–64 years who are employed, plus those who are unemployed.

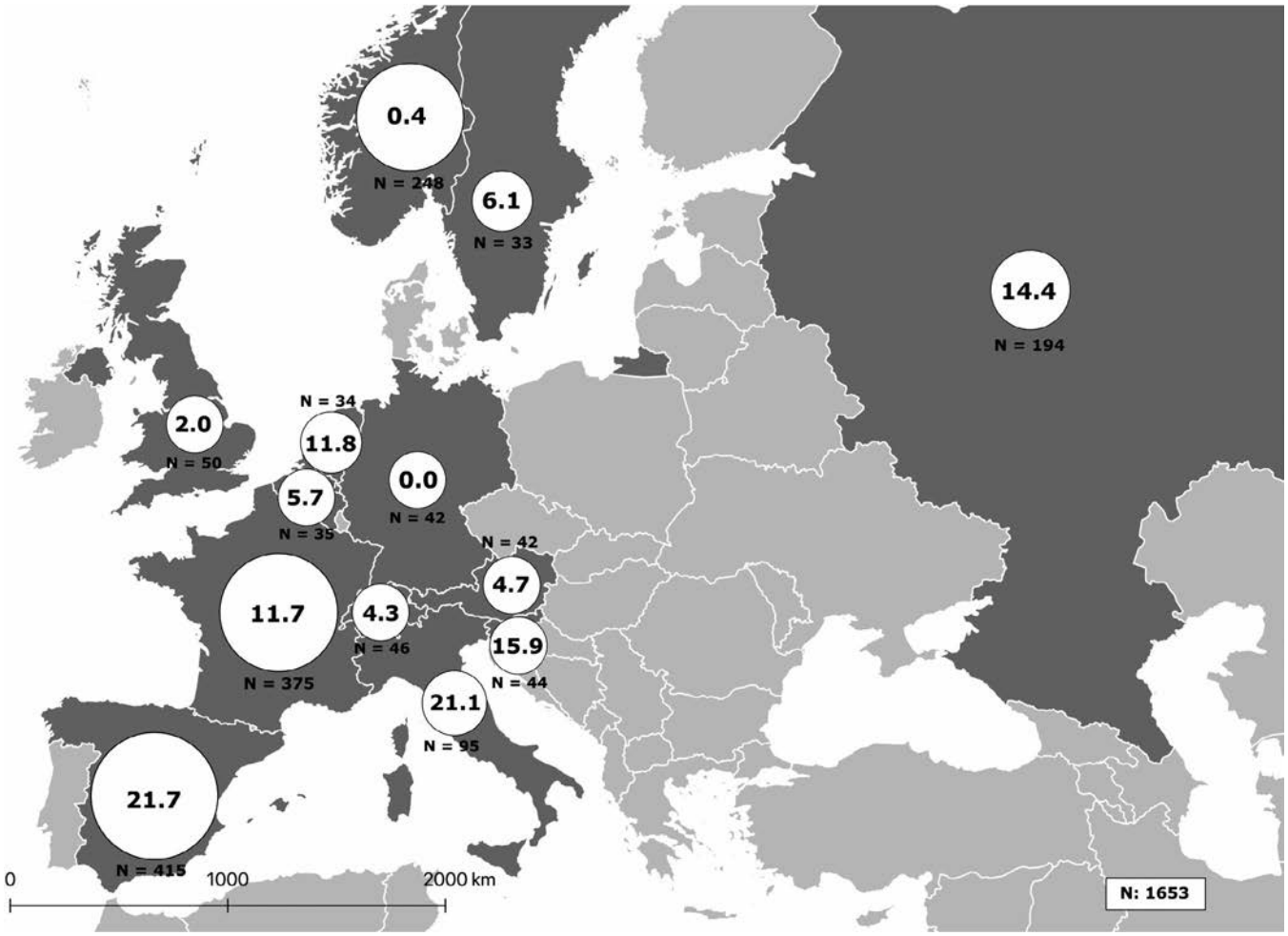

Figure 2. Unemployment rates reported by axial SpA patients in the labor force by country (n = 1,653).

by their condition. In all, 45.1% (1,084 of 2,405 participants who answered the survey item) reported "yes."

Of the 1,450 active and employed participants in the EMAS sample, 960 (67.7%) reported experiencing at least 1 WRI due to axial SpA in the past 12 months. Overall, 56.3% took sick leave, 44.6% had difficulties fulfilling working hours, 34% missed work due to doctor's appointments, 31.6% requested days off, 25.7% reduced their working hours, 18.9% changed work shift occasionally, 16.7% saw their professional life suffer, and 8.8% had to give up a previous job because of their axial SpA.

Active and employed patients with WRIs were more often female, more likely to have obtained a university education, and less likely to be married or in a relationship compared to active and employed patients without WRIs. Those with WRIs had higher disease activity (BASDAI) and higher levels of spinal stiffness, functional limitation, and psychological distress (GHQ-12). Furthermore, the presence of WRIs was associated with physical and psychological comorbidities (anxiety, depression). Patients with WRIs had a lower prevalence of IBD, while there was no difference in the prevalence of uveitis. No information on the presence of psoriasis was gathered across all of the EMAS-participating countries (Table 2).

The multivariate stepwise regression identified the following variables as an independent determinant of the WRIs in active and employed patients with axial SpA: higher BASDAI score (disease activity) and higher GHQ-12 score (psychological distress) (Table 3). Notably, cases included in the regression analysis were slightly older, had longer disease duration, and were more likely to have at least 1 physical comorbidity as compared to those excluded because of missing values of the explanatory variables. However, both samples had similar sociodemographic characteristics and patient-reported outcomes such as BASDAI or GHQ-12 scores.

DISCUSSION

The unemployment ratio of EMAS survey participants (12.3%) was almost double that of the European Union–28 zone for the year 2017 (6.8%), according to Eurostat (20). This trend is supported by other studies that compare employment

Table 2. Association between sociodemographic characteristics, patient-reported outcomes, and WRIs in active and employed participants*

Variable	WRIs (n = 960)	Without WRIs (n = 457)	*P*
Sociodemographic			
Age, years	41.2 ± 9.5	42.2 ± 10.3	0.085
Male, no. (%)	361 (37.6)	218 (47.7)	<0.001
Education level university, no. (%)	584 (60.8)	259 (56.7)	0.002
Married or with partner, no. (%)	772 (80.8)	377 (82.7)	0.406
Monthly income, €	1,219.4 ± 944.3	1,196.7 ± 920.3	0.945
Axial spondyloarthritis related			
Disease duration, years	15.0 ± 10.6	15.3 ± 10.8	0.666
BASDAI (0–10) (n = 1,303)	5.4 ± 1.8	4.0 ± 2.0	<0.001
Spinal Stiffness Index (3–12) (n = 1,349)	7.5 ± 2.4	6.3 ± 2.5	<0.001
Functional Limitation Index (0–54) (n = 1,396)	17.8 ± 15.4	16.5 ± 16.4	0.002
GHQ-12 (0–12) (n = 1,337)	5.1 ± 4.0	2.6 ± 3.3	<0.001
Uveitis (n = 1,298), no. (%)	168 (19.1)	75 (17.9)	0.581
Inflammatory bowel disease (n = 982), no. (%)	86 (13.0)	64 (20.1)	0.003
Comorbidities, no. (%)			
At least 1 physical comorbidity (n = 1,372)†	570 (61.2)	205 (46.6)	<0.001
Anxiety (n = 1,361)	298 (32.3)	71 (16.2)	<0.001
Depression (n = 1,364)	241 (26.1)	49 (11.1)	<0.001

* Values are the mean ± SD unless indicated otherwise. BASDAI = Bath Ankylosing Spondylitis Disease Activity Index. GHQ-12 = 12-Item General Health Questionnaire; WRI = work-related issues.
† Physical comorbidities considered were any severe infections requiring antibiotics in the past 12 months, any severe infections requiring inpatient hospital admission, atherosclerosis, cataracts, coronary artery disease, diabetes mellitus, episcleritis, fibromyalgia, genital lesions, glaucoma, gout, heart failure, hypercholesterolemia, hypertension, irregular heartbeat, kidney failure, liver disease, obesity, pacemaker fitted, psoriasis, psoriatic arthritis, and spinal or other fractures.

rates and absenteeism in patients with axial SpA to those of the general population (21). Despite the general trend for the whole of Europe indicated in this study, highlighting the disparity across the labor market in participating EMAS countries is important, with Mediterranean countries showing higher unemployment rates than those of Central and Northern Europe. As being unemployed is associated with worse health outcomes for patients with axial SpA, both in their physical and psychosocial health status (7,22) as well as their financial status, this situation points to the importance of national policies to prevent harmful consequences associated with diseases such as axial SpA.

Table 3. Univariate and multivariate stepwise logistic regression of the association between sociodemographic characteristics, patient-reported outcomes, and WRIs in active and employed participants*

Variable	Univariate logistic regression	Multivariate stepwise logistic regression
Age	0.99 (0.98–1.00)	NA
Female	1.51 (1.21–1.90)†	0.81 (0.61–1.08)
Education level, university	1.27 (1.07–1.50)†	NA
Marital status, married or with partner	0.88 (0.66–1.18)	NA
Monthly income, €	1.00 (1.00–1.00)	NA
BASDAI (0–10)	1.46 (1.36–1.56)†	1.30 (1.16–1.45)†
Spinal Stiffness Index (3–12)	1.22 (1.16–1.28)†	0.96 (0.89–1.04)
GHQ-12 (0–12)	1.21 (1.16–1.25)†	1.15 (1.08–1.22)†
Functional Limitation Index (0–54)	1.01 (1.00–1.01)	0.99 (0.98–1.01)
Uveitis	1.09 (0.81–1.47)	0.88 (0.56–1.39)
Inflammatory bowel disease	0.59 (0.41–0.84)†	0.58 (0.36–0.91)†
Any physical comorbidities	1.81 (1.44–2.27)†	0.98 (0.67–1.43)
Anxiety	2.47 (1.85–3.29)†	1.28 (0.76–2.14)
Depression	2.83 (2.03–3.94)†	0.99 (0.55–1.77)

* Values are the odds ratio (95% confidence interval). BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; GHQ-12 = 12-item General Health Questionnaire; NA = not applicable; WRIs = work-related issues.
† Statistically significant.

Some studies have reported that the rate of withdrawal from work is 3 times higher among patients with axial SpA than in the general population (23). The fact that more than one-half of EMAS participants of the inactive population reported either being on temporary or permanent sick leave reinforces the significant individual disability burden caused by axial SpA and its associated economic cost to society.

Furthermore, nearly two-thirds of the active employed population with axial SpA reported WRIs due to axial SpA. In more than one-half of the cases, patients took sick leave, approximately one-third missed work because of doctor appointments, one-fourth indicated that they had reduced their working hours, and nearly one-half reported difficulties in fulfilling working hours. These data support the fact that axial SpA is a disease that impacts significantly on working life, producing a variety of problems regarding absenteeism and presenteeism, compromising work productivity, and involving substantial direct and indirect costs to society (21).

Worse patient-reported outcomes, both physical and psychological, were associated with WRIs. In particular, higher disease activity as assessed by the BASDAI, and a higher level of psychological distress reflected by GHQ-12 scores, were identified as 2 independent predictors of WRIs in the multivariate regression analysis. Given the extensive research on the subject (2,4), the role of psychological distress (GHQ-12), which emerged as an important factor closely behind disease activity, is insufficiently explored (9). The relationship between physical and psychological health is complex and most likely bidirectional (24). In fact, an association between the BASDAI and GHQ-12 has been found in other studies (25). Most probably, disease activity by itself facilitates the triggering of WRIs while generating enough psychological distress to lead to greater WRIs.

Interestingly, the presence of IBD was negatively associated with the presence of WRIs, which may be related to a higher probability of being treated with biologic therapies in the presence of IBD, which could have had a positive impact on axial SpA activity. However, since no detailed information on current treatment was gathered, this possibility remains conjecture.

The present findings highlight the need for a holistic and interdisciplinary approach to axial SpA and related conditions in European countries, where health care should not focus solely on the clinical treatment of the disease. Stakeholders should recognize that patients with axial SpA take the disease to work and into their family and social life, all of which are also affected by it (26). Caring about the working life of axial SpA patients, providing workplace adaptations, and ensuring flexibility at work will lead to better health outcomes and ultimately a higher quality of life for those with this chronic condition.

This study is not without limitations. First, we acknowledge that it did not use previously validated scales or indices in assessing the impact on work or functional impairment. The decision was taken during the preliminary phase of the survey development, when patients expressed concern about the limitations of existing measures that did not capture all aspects of their disease; therefore, the survey questions may reflect other, but relevant, issues for the patients not reported in previous studies. Second, the study may be subject to sample bias, since data from some countries concentrated a high percentage of the total participants, such as Spain, France, or Norway. In any case, these countries represent a wide range of possible unemployment outcomes in Europe, so this effect is probably counter-weighted. Furthermore, a higher proportion of female participants in some countries might reflect a higher proportion of female members in the patient organization and not necessarily in the axial SpA population.

Approximately 50% of the patients were excluded from the multivariable analysis due to missing values of those variables included in the model, which represents another potential source of a sample bias. At the same time, the main sociodemographic characteristics and patient-reported outcome parameters were similar across excluded and included patients, which makes the risk of the bias rather low. Finally, despite the bidirectional nature of associations reported, another limitation of this study is the inability to establish causality using this cross-sectional approach. In fact, assessing the cause of WRIs is difficult, whether due to the problems related to the disease, the underlying inflammatory processes, or other factors associated with this chronic pathology (spinal stiffness or functional limitations in daily life). We can only conclude that relationships exist between these variables. To establish causality, we would need to carry out longitudinal studies regarding the evolution of physical and psychological variables and their relationship to work productivity or vice versa. Finally, the possible effect of pharmacologic treatments on work productivity could have influenced the results of our study in ways we had not anticipated.

Axial SpA has a substantial impact on working life, with disease-associated WRIs reported by two-thirds of the active employed population in this study. High disease activity and significant levels of psychological distress were 2 major independent determinants of WRIs. Overall, there is a need for a holistic approach to axial SpA care to ensure that patients have the support needed to remain part of the workforce and retain autonomy over their professional future.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Garrido-Cumbrera had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Garrido-Cumbrera, Bundy, Navarro-Compán, Makri, Mahapatra, Delgado-Domínguez, Poddubnyy.

Acquisition of data. Garrido-Cumbrera, Bundy, Navarro-Compán, Makri, Sanz-Gómez, Christen, Mahapatra, Delgado-Domínguez, Poddubnyy.

Analysis and interpretation of data. Garrido-Cumbrera, Bundy, Navarro-Compán, Makri, Sanz-Gómez, Christen, Mahapatra, Delgado-Domínguez, Poddubnyy.

ROLE OF THE STUDY SPONSOR

Novartis Pharma AG had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Novartis Pharma AG.

REFERENCES

1. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017;390: 73–84.
2. Espahbodi S, Bassett P, Cavill C, Freeth M, Hole J, Sengupta R. Fatigue contributes to work productivity impairment in patients with axial spondyloarthritis: a cross-sectional UK study. Clin Exp Rheumatol 2017;35:571–8.
3. Molto A, Tezenas du Montcel S, Wendling D, Dougados M, Vanier A, Gossec L. Disease activity trajectories in early axial spondyloarthritis: results from the DESIR cohort. Ann Rheum Dis 2017;76:1036–41.
4. Ramonda R, Marchesoni A, Carletto A, Bianchi G, Cutolo M, Ferraccioli G, et al. Patient-reported impact of spondyloarthritis on work disability and working life: the ATLANTIS survey. Arthritis Res Ther 2016;18:78.
5. Haglund E, Petersson IF, Bremander A, Bergman S. Predictors of presenteeism and activity impairment outside work in patients with spondyloarthritis. J Occup Rehabil 2015;25:288–95.
6. Hooge M de, Ramonda R, Lorenzin M, Frallonardo P, Punzi L, Ortolan A, et al. Work productivity is associated with disease activity and functional ability in Italian patients with early axial spondyloarthritis: an observational study from the SPACE cohort. Arthritis Res Ther 2016;18:265.
7. Healey EL, Haywood KL, Jordan KP, Garratt A, Packham JC. Impact of ankylosing spondylitis on work in patients across the UK. Scand J Rheumatol 2011;40:34–40.
8. Van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van Den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978–91.
9. Packham J. Optimizing outcomes for ankylosing spondylitis and axial spondyloarthritis patients: a holistic approach to care. Rheumatology (Oxford) 2018;57:vi29–34.
10. Chorus AM, Boonen A, Miedema HS, van der Linden S. Employment perspectives of patients with ankylosing spondylitis. Ann Rheum Dis 2002;61:693–9.
11. Montacer Kchir M, Mehdi Ghannouchi M, Hamdi W, Azzouz D, Kochbati S, Saadellaoui K, et al. Impact of the ankylosing spondylitis on the professional activity. Jt Bone Spine 2009;76:378–82.
12. Garrido-Cumbrera M, Poddubnyy D, Gossec L, Gálvez-Ruiz D, Bundy C, Mahapatra R, et al. The European Map of Axial Spondyloarthritis: capturing the patient perspective. An analysis of 2846 patients across 13 countries. Curr Rheumatol Rep 2019;21:19.
13. Garrido-Cumbrera M, Navarro-Compán V, Zarco P, Collantes-Estévez E, Gálvez-Ruiz D, Braçe O, et al. Atlas of axial spondyloarthritis in Spain 2017: study design and population. Reumatol Clin 2019;15:127–32.
14. Garrido Cumbrera M, Gálvez Ruiz D, Chacón García J, Braçe O, Villoro Valdés R, Merino Ventosa M, et al. Atlas of axial spondyloarthritis in Spain 2017: profile of the disease. Heidelberg: Max Weber Institute; 2017.
15. International Labour Organization. Labour force. 2019. URL: https://www.ilo.org/global/statistics-and-databases/statistics-overview-and-topics/WCMS_470304/lang--en/index.htm.
16. Pasteels JM. ILO Projections of the economically active population: revised methodology of the 2011 edition. 2012. URL: https://www.ilo.org/wcmsp5/groups/public/---dgreports/---stat/documents/publication/wcms_213752.pdf.
17. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
18. Goldberg DP, Williams P. A user's guide to the General Health Questionnaire. Berkshire (UK): NFER-Nelson; 1988.
19. Cano A, Sprafkin RP, Scaturo DJ, Lantinga LJ, Fiese BH, Brand F. Mental health screening in primary care: a comparison of 3 brief measures of psychological distress. Prim Care Companion J Clin Psychiatry 2001;3:206–10.
20. EUROSTAT. Employment statistics. 2018. URL: http://ec.europa.eu/eurostat/statistics-explained/index.php/Employment_statistics.
21. Boonen A. A review of work-participation, cost-of-illness and cost-effectiveness studies in ankylosing spondylitis. Nat Clin Pract Rheumatol 2006;2:546–53.
22. Marengo MF, Schneeberger EE, Citera G, Cocco JA. Work status among patients with ankylosing spondylitis in Argentina. J Clin Rheumatol 2008;14:273–7.
23. Boonen A, van der Linden SM. The burden of ankylosing spondylitis. J Rheumatol Suppl 2006;78:4–11.
24. Jang JH, Green CE, Assassi S, Reveille JD, Ward MM, Weisman MH, et al. The contribution of disease activity on functional limitations over time through psychological mediators: a 12-month longitudinal study in patients with ankylosing spondylitis. Rheumatology (Oxford) 2011;50:2087–92.
25. Garrido-Cumbrera M, Delgado-Domínguez CJ, Gálvez-Ruiz D, Blanch Mur C, Navarro-Compán V. The impact of axial spondyloarthritis on mental health: results from the Atlas. J Rheumatol 2019;46:1284–9.
26. Ward MM, Reveille JD, Learch TJ, Davis JC Jr, Weisman MH. Impact of ankylosing spondylitis on work and family life: comparisons with the US population. Arthritis Rheum 2008;59:497–503.

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Impact of Disease Activity on Physical Activity in Patients With Psoriatic Arthritis

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Objective. The purpose of this study was to compare physical activity (PA) in a group of patients with psoriatic arthritis (PsA) versus healthy controls and to determine whether the mobility of these patients is affected by disease activity.

Methods. A group of 52 patients with PsA and 53 controls were included in this case–control study. PA was assessed by accelerometry in both groups and additionally with the International Physical Activity Questionnaire (IPAQ) in patients with PsA. Multiple regression analysis was used to compare PA between groups and to determine the relationship between PA and PsA features, including disease activity, as assessed by the 28-joint Disease Activity Score (DAS28) and the Disease Activity Index for Psoriatic Arthritis (DAPSA) score. In a group of 36 patients, a test–retest study was carried out after 6 months.

Results. The time engaged in moderate-to-vigorous physical activity (MVPA) per day, as evaluated by accelerometry, and adjusted by confounders, proved similar in patients with PsA and controls. In patients with PsA, disease activity was inversely related to PA as assessed either by IPAQ or accelerometry. When PA was compared in patients with PsA between the 2 visits, a significant difference in the amount of time doing MVPA was found (42 ± 33 versus 30 ± 22 minutes/day; $P = 0.004$). Interestingly, in the test–retest study, variations in disease activity over time based on DAPSA scores (r = –0.49, $P = 0.002$) and DAS28 using the C-reactive protein level (r = –0.4, $P = 0.017$) were inversely correlated with changes in PA, as determined by accelerometry.

Conclusion. Patients with PsA show levels of PA like healthy controls. In patients with PsA, disease activity and PA are inversely correlated and the evaluation of PA by accelerometry is sensitive to changes in disease activity.

INTRODUCTION

Although extensive data show the beneficial effects of physical activity (PA) on cardiovascular disease and all-cause mortality, sedentarism is a major health problem worldwide (1,2). Although PA assessment is complex, viable and accessible methods for its assessment are now available (3). These include questionnaires and triaxial accelerometers, tools that are gaining increasing acceptance for assessing PA, both in healthy individuals and in patients with chronic diseases (4–6). Although questionnaires are susceptible to issues of subjectivity, the International Physical Activity Questionnaire (IPAQ) has been used mainly for researching several conditions, including rheumatic diseases (5,7,8). Alternatively, accelerometers are easily portable devices that offer one important advantage in objectively measuring PA. This advantage stems from the fact that they can continuously capture distinctive characteristics of movement for days or even weeks (9,10). Although accelerometry has already been used in clinical trials for osteoarthritis (11,12), only recently was this technique used to evaluate PA patterns in inflammatory joint disorders such as rheumatoid arthritis (RA) or systemic lupus erythematosus (8,13–16).

In RA, different objective and subjective methods for evaluating PA have revealed that these patients tend to exercise less than what is currently recommended (17–19). A multinational study for RA patients involving a self-reporting questionnaire demonstrated that 60–80% of patients were physically inactive. In that study, physical inactivity was associated with low functional capacity and higher levels of disease activity, pain, and fatigue (18). When

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- Accelerometry is a valid technique for assessing physical activity in patients with psoriatic arthritis (PsA).
- Physical activity in patients with PsA is comparable to that performed by healthy controls.
- Changes in disease activity of patients with PsA are inversely related to variations in accelerometer-assessed physical activity.

PA is objectively assessed by accelerometry, the main disparity between RA patients and healthy individuals can be seen in the time devoted to different intense activities: RA patients spend less time engaging in moderate-to-vigorous PA (MVPA) than healthy controls (8,13–15,20).

Psoriatic arthritis (PsA), like RA, is a chronic inflammatory arthropathy of the peripheral joints that differs in certain clinical and radiologic characteristics relating to axial inflammation and the presence of psoriasis. Although patients who develop PsA are known to experience a compromised quality of life and an inability to perform many daily activities (21), surprisingly, no studies have focused on evaluating PA in these patients with respect to controls, using either subjective or objective methods. In addition, the influence of disease activity on PA and vice versa on patients with PsA remains to be fully clarified (22). Regarding axial spondyloarthropathies, using both objective and subjective measures, the evidence suggests that disease activity is inversely correlated with PA, though the evidence is less clear when comparing the basal PA of these patients with healthy controls (23,24). The main purposes of this study were to compare PA in a group of patients with PsA versus healthy controls through both objective (accelerometry) and subjective (IPAQ) methods and to explore the relationship between disease activity and PA in these patients.

PATIENTS AND METHODS

Study design. Anthropometric characteristics, comorbidities, and PA (as described later) were studied in both patients with PsA and controls in the initial visit. At the same time, clinical disease activity was also assessed in the PsA group. In addition to the initial assessment, the group of patients with PsA was informed that a reevaluation of PA would be carried out 6 months later. The institutional review board (Comité Etico de Investigación Clínica del Hospital Universitario de Canarias; 2016_88, PSORIAF study) approved this study, and all patients and controls signed a written informed consent.

Sample size. The number of patients recruited for this research was based on the results of a preliminary study. We assessed PA in 15 patients with PsA and 15 controls over 5 consecutive days (3 workdays and 1 full weekend) using accelerometry. The reference group engaged in MVPA an average of 33 minutes per day and the patient group 23 minutes per day, with a common SD of 23. To achieve 80% power in our ability to detect any differences in the contrast null hypothesis (H0:m1 = m2) using a bilateral Student's *t*-test for 2 independent samples, with a 5% significance level, 42 patients had to be included in the experimental group and 42 patients in the control group.

Study participants. For this case–control study, 70 patients with PsA who attended the rheumatology service outpatient room consecutively between January and February 2017 were invited to participate. From January to September 2017 this group of patients was assessed. The patient recruitment flow chart is shown in Figure 1. Inclusion criteria for patients with PsA were men or women age 18–65 years and confirmation by a rheumatologist as having fulfilled the Classification of Psoriatic Arthritis Study Group criteria for PsA (25). Exclusion criteria were: 1) patients with joint deformities of any origin in the large joints of the lower extremities at the time of enrollment, as assessed by anamnesis and physical exploration, or who had undergone any type of joint surgery in the legs and/or hips, as stated in their medical records; 2) patients with Steinbrocker's classification of functional capacity class III and IV; and 3) patients with comorbidities that negatively influenced their capability for PA, such as pulmonary and/or cardiovascular disease, peripheral vascular disease, or residual lower-extremity neuromuscular effects from stroke. No medication restrictions were imposed on patients with PsA included in this study.

Fifty-three controls were recruited among relatives who shared a family environment with the patients with PsA included in this study. After controls agreed to participate in the study and signed the informed consent, the presence of inflammatory arthropathy was ruled out by anamnesis. Six months after the initial assessment, a new evaluation of disease activity and PA by accelerometry using the same indexes and procedures as the initial visit was done with 36 patients with PsA who agreed to participate in a second visit.

Data collection. All subjects, both patients and controls, completed a medication questionnaire and underwent a physical examination. Weight, height, body mass index (BMI as kg/m^2), and systolic and diastolic blood pressure were assessed under standardized conditions. Information regarding smoking status (current smoker versus nonsmoker), diabetes mellitus, and hypertension was obtained from the questionnaire. Medical records were reviewed to ascertain specific diagnoses and medications. At the time of assessment, disease activity in patients with PsA, as well as PA in both patients and controls, was measured as described below. In patients with PsA, any history of therapy with glucocorticoids, classic synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate, and biologic DMARDs (bDMARDs) was collected.

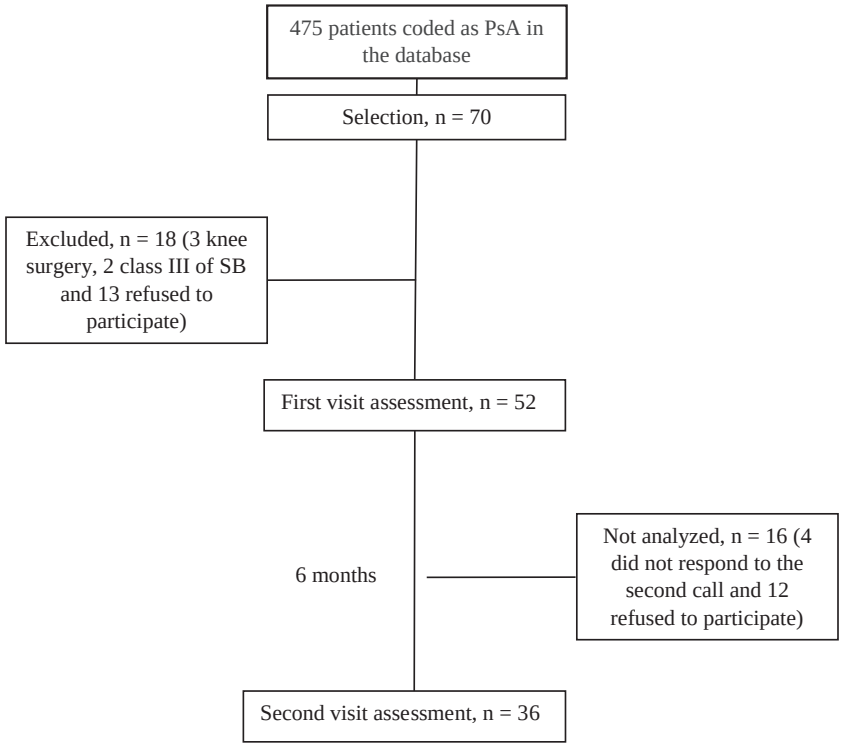

Figure 1. Recruitment flow diagram. PsA = psoriatic arthritis; SB = Steinbrocker classification of functional capacity.

PsA clinical assessment. In patients with PsA, disease activity was measured using the 28-joint Disease Activity Score (DAS28) using the erythrocyte sedimentation rate (ESR) or the C-reactive protein (CRP) level (DAS28-ESR or DAS28-CRP) (26) and the Disease Activity Index for Psoriatic Arthritis (DAPSA) scale (27). In the group of patients with PsA whose disease activity was reevaluated, variations in DAS28 (ΔDAS28) were expressed according to the following equation: $\Delta DAS28 = DAS28_{final} - DAS28_{initial}$; variations in DAPSA (ΔDAPSA) were calculated using the equation: $\Delta DAPSA = DAPSA_{final} - DAPSA_{initial}$. DAS28 improvement was defined as a reduction in basal DAS28 >1.2 points according to European Alliance of Associations for Rheumatology criteria (28). Patients with PsA were defined as being in clinical remission (DAPSA score <4) or having low (DAPSA score 5–14), moderate (DAPSA score >15 to 28) or high disease activity (DAPSA score >28) as previously described (29). Disease disability was assessed by the Health Assessment Questionnaire (HAQ) (30). Fatigue was measured using the Functional Assessment of Chronic Illness Therapy (FACIT) questionnaire (31).

PA assessment. PA was assessed by both objective (accelerometry) and subjective (IPAQ) methods. Patients were provided with the IPAQ long form (5), and data were collated and presented both as median minutes per week or median metabolic equivalent-of-task (MET) minutes per week and as categorical cut point values (defined as low, moderate, and high) following the guidelines for data processing and analysis outlined on the IPAQ website (http://www.ipaq.ki.se/scoring.pdf). The questionnaire was administered immediately after the accelerometry measurement to evaluate the previous week, including the 5 days in which the device was used.

For the objective assessment of PA, we used the Actigraph-GT3X accelerometer, a portable electronic device that continuously measures acceleration along 3 axes (6). Both patients and healthy controls were instructed to carry the accelerometer by means of an elastic waistband on the left hip. Accelerometry data were recorded continuously over 5 days (3 workdays and 1 full weekend) at a sampling frequency of 1 minute/subject, and output was expressed in a counts-per-minute vector. No instructions were given to the subjects regarding their specific performance of PA. The time spent at the 4 activity levels was determined based on published cut points: sedentarism (0–99 counts/minute), light activity (100–2,019 counts/minute), moderate activity (2,020–5,998 counts/minute), and vigorous activity (≥5,999 counts/minute) (32). Therefore, in our study, accelerometer data used to evaluate PA were as follows: total kilocalories (sum of activity and basal kilocalories) per day; activity kilocalories per day; number of sedentary minutes per day; number of light, moderate, and vigorous activity minutes per day; number of moderate-to-vigorous activity minutes per day (MVPA); total vector magnitude (in counts/minute, including active and resting times); and average total counts per day. According to the information provided by the manufacturer, the energy expenditure was calculated by the accelerometer using several algorithms based

on the work of Freedson et al (33) that predict energy expenditure from activity counts and body mass.

From the group of patients initially recruited, 36 were reevaluated 6 months later; for the other 16 patients, retesting was not possible for various reasons as described in the recruitment flow chart (Figure 1). Variations in minutes in MVPA (ΔMVPA) were expressed according to the equation: $\Delta MVPA = MVPA_{final} - MVPA_{initial}$.

Statistical analysis. The demographic and clinical characteristics of patients with PsA and controls were compared using a chi-square test for categorical variables or a Student's *t*-test for continuous variables (data are expressed as mean ± SD). For noncontinuous variables, a Mann-Whitney U test was performed or a logarithmic transformation was carried out and data were expressed as the median (interquartile range). Since the values for IPAQ and accelerometry are expressed differently, an intraclass correlation coefficient was not feasible for a concordance analysis comparing the 2 methods. Thus, both were divided into terciles, and a quadratically weighted kappa index was calculated. Correlations between PA and clinical features of PsA, as well as comparisons between patients with PsA and controls, were performed through multivariate analysis, adjusting for age, sex, BMI, and work activity. A second evaluation of disease activity and PA by IPAQ score and accelerometry was conducted 6 months after the initial visit. Because none of the general characteristics of patients with PsA, including smoking status, changed between the 2 visits, no statistical adjustment for confounders was made. The association between variations in the DAPSA and DAS28 indices, and PA, as measured by accelerometry, was analyzed using Pearson's correlation. All analyses used a 5% 2-sided significance level and were performed using SPSS software, version 24. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the participants. Table 1 shows the general and disease-related characteristics of the participants in this study. In our series, patients exhibited low disease levels as illustrated by the DAS28-ESR and DAS28-CRP and moderate levels by DAPSA score. Half of the patients were undergoing treatment with bDMARDs, almost 75% with a csDMARD, and only one-fourth with prednisone. There were no differences between patients and controls regarding age, sex, BMI, the presence of hypertension, metabolic syndrome, labor activity, or level of education.

Comparison of PA in patients and controls. As measured by accelerometry, there were no differences between patients and controls in terms of activity kilocalories per day, total kilocalories per day, global vector magnitude, average total counts per day, time spent in sedentarism or in low, moderate, and vigorous activity, or in MVPA per day (Table 1). When PA of patients with moderate or high disease activity, assessed by either DAPSA (>15, n = 24) or DAS28-CRP (>3.2, n = 17) were compared with controls, the average minutes spent doing MVPA (33 ± 25 and 29 ± 18 minutes, respectively) was also not significantly different from controls (38 ± 16 minutes; $P = 0.307$ and $P = 0.10$, respectively).

Agreement between accelerometry and IPAQ data. When accelerometry was assessed in patients with PsA, either by MVPA or by kilocalories per day, and IPAQ was assessed by MET minutes/week categorized into tertiles, agreement was evident to a moderate degree, with a median quadratic weighted kappa index of 0.27 (95% confidence interval [95% CI] 0.017, 0.524; $P = 0.05$) and 0.24 (95% CI –0.018, 0.510; $P = 0.07$), respectively. Other accelerometry parameters such as total kilocalories per day, total vector magnitude, active vector magnitude, average total counts per day, number of low activity minutes per day, number of moderate activity minutes per day, and number of vigorous activity minutes per day did not correlate with IPAQ (MET minutes/week) in patients with PsA (data not shown).

Relationship between PA and disease symptoms in patients with PsA. Table 2 shows the relationship between PA, as assessed by IPAQ and accelerometry, and anthropometric data, disease activity, medication, and fatigue in patients with PsA. While BMI was inversely related with vector magnitude and time in MVPA (as measured by accelerometry), age, and waist-to-hip ratio showed no correlation with PA (as assessed by either method). Disease activity, as assessed by DAS28-CRP or DAS28-ESR and by DAPSA, negatively correlated with IPAQ and time in MVPA, as determined by accelerometry. On the other hand, ESR, but not CRP level, was inversely associated with time in MVPA and kcal/day expenditure by accelerometry. However, none of these acute-phase reactants showed any association with PA as assessed by IPAQ. The HAQ score negatively correlated with IPAQ but not with any of the accelerometer parameters evaluated. Remarkably, corticoids intake (as a binary variable) showed a positive correlation with all accelerometer parameters evaluated, but not with IPAQ. In contrast, FACIT did not correlate with PA when assessed by either method in our group of patients.

Effects of disease activity on PA in patients with PsA. To determine whether the level of PA observed in patients with PsA was associated with disease activity, a second assessment of PA and disease activity was performed in a randomized group of 36 patients 6 months after the basal visit. Table 3 shows the PA data for this group of patients, as assessed by IPAQ or accelerometry under the same conditions for both visits. Overall, as measured by accelerometry, patients engaged in significantly less PA, including less time in MVPA ($P = 0.004$) at the second visit comparted to the initial one. The IPAQ (METs/day) detected the same tendency of PA between the 2 visits, albeit without reaching

Table 1. Basal characteristics of patients and controls*

Characteristics	PsA patients (n = 52)	Controls (n = 53)	*P*
Women, no. (%)	25 (47)	26 (51)	0.20
Age, years	53 ± 13	50 ± 8	0.16
Level of education, no. (%)	–	–	0.15
Elementary	30 (57)	22 (42)	–
Postsecondary education	23 (43)	30 (58)	–
Body mass index, kg/m^2	28 ± 5	26 ± 4	0.085
Hypertension, no. (%)	22 (41)	18 (35)	0.47
Diabetes mellitus, no. (%)	9 (17)	5 (10)	0.27
Tobacco use, no. (%)	11 (21)	8 (16)	0.48
Work activity, no. (%)	25 (47)	26 (51)	0.63
Metabolic syndrome, no. (%)	19 (36)	–	–
PsA features			
Disease duration, years	11 ± 7.5	–	–
Psoriasis duration, years	16 ± 13	–	–
HAQ	0.750 ± 0.660	–	–
DAS28-ESR	2.96 ± 1.36	–	–
DAS28-CRP	2.67 ± 1.19	–	–
DAPSA	17 ± 12	–	–
SJC, mean [IQR]	1 [1]	–	–
TJC, mean [IQR]	4 [6]	–	–
ESR, mm/hour	17 ± 16	–	–
CRP, mg/liter	5.4 ± 7.3	–	–
Corticosteroids, no. (%)	12 (23)	–	–
DMARDs, no. (%)	38 (72)	–	–
Biologic treatment, no. (%)	26 (49)	–	–
FACIT	1.35 ± 0.79	–	–
Accelerometry			
Total kcal/day	2,417 ± 1,440	2,001 ± 819	0.073
Activity, kcal/day	408 ± 237	356 ± 146	0.18
Total count	2,594,231 ± 1,433,148	2,449,614 ± 663,048	0.51
Counts per minute	376 ± 196	364 ± 99	0.69
Minutes sedentary/day	1128 ± 208	1,154 ± 147	0.46
Minutes light activity/day	170 ± 73	169 ± 48	0.90
Minutes moderate activity/day	45 ± 33	37 ± 15	0.099
Minutes vigorous activity/day	1.3 ± 4.3	1.2 ± 2.2	0.88
MVPA/day	47 ± 35	38 ± 16	0.11

* Values are the mean ± SD unless indicated otherwise. Total kcal/day is the sum of basal and activity kilocalories (kcal) per day. CRP = C-reactive protein; DAPSA = Disease Activity in Psoriatic Arthritis; DAS28 = 28-joint Disease Activity Score; DMARDs = disease-modifying antirheumatic drugs; ESR = erythrocyte sedimentation rate; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = Health Assessment Questionnaire; IQR = interquartile range; MVPA = moderate-to-vigorous physical activity; PsA = psoriatic arthritis; SJC = swollen joint count; TJC = tender joint count.

statistical significance. Figure 2 shows composite plots of the variations in DAPSA, DAS28-CRP, and DAS28-ESR with respect to MVPA (minutes/week), obtained by subtracting the values of the second visit from the basal visit for all patients in this group. A significant inverse correlation was observed between DAPSA and MVPA (r = –0.49, $P = 0.002$) and between DAS28-CRP and MVPA (r = –0.4, $P = 0.017$). The same analysis to evaluate PsA activity using DAS28-ESR also showed an inverse correlation with PA, though it did not reach statistical significance (r = 0.34, $P = 0.070$).

DISCUSSION

The most important findings of our work can be summarized as follows: 1) patients with PsA show a daily PA similar to healthy controls as assessed by IPAQ and accelerometry; 2) in these patients, PA, as measured by either method, is inversely associated with disease activity, as determined by DAS28 or DAPSA; and, more interestingly, 3) over time, variations in disease activity in patients with PsA inversely correlated with changes in PA as assessed by accelerometry in terms of time in MVPA.

Regular exercise of moderate-to-high levels of intensity has proven to be effective in improving muscle strength and cardiovascular fitness in healthy populations and in patients with chronic illnesses, including patients with RA and psoriasis (2,19,34,35). Because PsA is a chronic joint disease that leads to deformity and joint destruction, it has been assumed that patients with this disorder, as happens in RA (8,13–15,20), are less active than the general population. However, no study has analyzed PA in patients

Table 2. Multivariate analysis of PsA features and PA as assessed by accelerometry and the International Physical Activity Questionnaire (IPAQ)*

Characteristics (n = 52)	IPAQ				Accelerometry			
	MET, minutes/week	*P*	Total vector magnitude, counts/minute	*P*	MVPA, minutes/day	*P*	Activity, kcal/day	*P*
Age, years	−14.6 (−139, 110)	0.8	−1.25 (−5.59, 3.09)	0.56	−0.79 (−4.64, 3.06)	0.68	0.74 (−4.45, 5.93)	0.77
Body mass index, kg/m^2	−144 (−471, 182)	0.38	−11.97 (−22.44, −1.49)	0.03†	−9.57 (−19.42, 0.26)	0.05†	5.62 (−7.34, 18.57)	0.38
Waist:hip ratio	−3,346 (−21,175, 14,483)	0.71	−489 (−1,099, 120)	0.11	−59.81 (−701, 581)	0.85	533 (−218, 1,283)	0.16
Disease activity								
ESR, mm/hour	−3.37 (−103, 96.2)	0.94	−2.55 (−5.93, 0.82)	0.14	−3.66 (−6.56, −0.77)	0.01†	−4.42 (−8.37, −0.47)	0.03†
CRP, mg/liter	−51.21 (−270, −167)	0.64	−6.06 (−13.47, 1.35)	0.1	−5.39 (−12.03, 1.26)	0.11	−5.65 (−14.5, 3.19)	0.20
SJC, no.	−229 (−1292, 833)	0.67	12.98 (−23.48, 49.45)	0.48	−1.07 (−34.16, 32.01)	0.95	−4.08 (−47.62, 39.45)	0.85
TJC, no.	−242 (−472, −8)	0.04†	0.94 (−8.39, 10.26)	0.84	−1.59 (−9.94, 6.75)	0.7	−0.68 (−12.29, 10.92)	0.90
DAS28-ESR	−1,120 (-2,264, 24)	0.05†	−15.55 (−58.42, 27.32)	0.47	−44.00 (−80.22, −7.78)	0.02†	−52.91 (−105, −0.82)	0.04†
DAS28-CRP	−1,504 (−2,769, −240)	0.02†	−10.53 (−59.05, 37.98)	0.66	−41.61 (−83.10, −0.14)	0.04†	−40.18 (−97.82, 17.46)	0.17
DAPSA	−133 (−254, −12)	0.03†	−2.31 (−688, 2.26)	0.31	−4.76 (−8.63, −0.88)	0.02†	−4.96 (−10.26, 0.33)	0.06
HAQ	−3,410 (−5,629, −1,189)	0.003†	−27.96 (−114, 58.51)	0.52	−50.55 (−126, 25.26)	0.18	−37.88 (−141, 65.99)	0.47
Disease duration, years	32.36 (−176, 241)	0.76	−6.44 (−13.53, 0.65)	0.07	−5.72 (−12.02, 0.56)	0.07	−5.30 (−13.90, 3.29)	0.22
Corticoids intake	4,173 (−5,246, 13,592)	0.28	417 (215, 618)	0.003†	447 (166, 727)	0.01†	192 (11.72, 373)	0.04†
FACIT fatigue	−590 (−2,600, 1,419)	0.5	−5.77 (−77.77, 66.22)	0.87	−44.52 (−107, 18.12)	0.16	−30.13 (−115, 55.01)	0.48

* Values are the β coefficient (95% confidence interval) unless indicated otherwise. Data were adjusted for sex, age, body mass index, and work activity. CPR = C-reactive protein; DAPSA = Disease Activity in Psoriatic Arthritis; DAS28 = 28-joint Disease Activity Score; ESR = erythrocyte sedimentation rate; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = Health Assessment Questionnaire; kcal = kilocalories; MET = metabolic equivalent of task; MVPA = moderate-to-vigorous physical activity; PA = physical activity; PsA = psoriatic arthritis; SJC = swollen joint count; TJC = tender joint count.
† Statistically significant at $P < 0.05$.

Table 3. Physical activity between visits*

	Physical activity, visit 1 (n = 36)	Physical activity, visit 2 (n = 36)	*P*
Accelerometry			
Total kcal/day	2,260 ± 1,481	1,920 ± 1,250	0.066
Activity kcal/day	385 ± 244	448 ± 776	0.64
Total count	2,450,169 ± 1,193,459	2,340,146 ± 1,177,417	0.53
Counts per minute	362 ± 160	333 ± 168	0.22
Minutes sedentary/day	1,134 ± 143	1,227 ± 238	0.049†
Minutes light activity/day	168 ± 52	172 ± 71	0.79
Minutes moderate activity/day	42 ± 32	36 ± 27	0.077
Minutes vigorous activity/day	1 ± 1.2	2 ± 8	0.36
Minutes in MVPA/day	42 ± 33	30 ± 22	0.004†
Total kcal, activity + basal kcal	2,260 ± 1,481	1,920 ± 1,250	0.066
IPAQ			
METs/day	6,115 ± 6,024	4,453 ± 3,834	0.067
Categorized, no. (%)			0.71
Low activity	2 (4)	2 (5)	0.99
Moderate activity	18 (35)	15 (34)	0.99
Vigorous activity	33 (61)	26 (61)	0.99

* Values are the mean ± SD unless indicated otherwise. Total kcal/day is the sum of basal and activity kilocalories (kcal) per day. IPAQ = International Physical Activity Questionnaire; MET = metabolic equivalent of task; MVPA = moderate-to-vigorous physical activity.
† Statistically significant.

with PsA compared to healthy controls using objective techniques. This gap prompted us to analyze PA levels, both objectively (by accelerometry) and subjectively (by IPAQ), in a group of patients with PsA, comparing them with age- and sex-matched healthy controls. To avoid any interference with PA evaluations, specifically with accelerometry, patients with previous surgical intervention or disability by any reason in their lower-extremities were excluded from this study. Therefore, our results cannot be extrapolated to the general population of patients with PsA, although they nevertheless constitute a model for studying the relationship between disease activity and PA in patients with PsA.

Questionnaire-based surveys, as well as studies using accelerometers, have shown that patients with RA tend to exercise less than what is currently recommended (17–19). The main disparity in the PA of patients with RA compared to healthy controls is that the former dedicate less time than controls to engaging in MVPA (8,13–15,20). Based on this, as well as on the preliminary results of our pilot study for sample size calculation, we expected that patients with PsA would show lower PA than controls in terms of time spent engaged in MVPA, as assessed by accelerometry. However, at the end of the study, accelerometry data showed that patients with PsA and healthy patients did not differ significantly in their PA levels after adjusting by such confounders as age, sex, BMI, or work status. In contrast, a previous work with the same methodology demonstrated that patients with RA exerted less MVPA than controls (8). A possible explanation for this finding could be that the overall disease activity of patients with PsA included in our study was low-moderate (DAS28-ESR mean ± SD 2.96 ± 1.36 and DAPSA score 17 ± 12). Nevertheless, patients with moderate-high disease activity did not show significant differences compared to controls in terms of minutes spent doing MVPA, as evaluated by accelerometry. Furthermore, for the interpretation of these data, note that controls and patients shared the same family environment, a characteristic that reinforces the idea that PsA by itself does not seem to negatively influence patients' PA.

Unfortunately, the lack of previous studies analyzing PA in patients with PsA versus healthy individuals by means of IPAQ or accelerometers precludes any direct comparisons of our results with those of other studies. However, the results of a previous report that used a different questionnaire to assess PA and standardized PA data as comparator point in the same direction as our study. A 2009 Swedish cross-sectional postal questionnaire of spondylarthritis patients (36) showed that patients with PsA met World Health Organization recommendations for time engaged in moderate, but not in vigorous, PA (37). Unlike PsA, PA has been studied in patients with psoriasis using IPAQ (38) and accelerometry (39), albeit with contradictory conclusions. Some studies suggest that PA has an inverse relationship with both the extent and severity of psoriasis (39,40); others have found no difference when comparing patients with psoriasis with individuals without psoriasis (41,42). In fact, a study using accelerometry even shows greater PA in the group with psoriasis compared to controls (43).

Questionnaires have been shown to be less reliable than accelerometers in assessing total energy expenditure under various conditions (44,45). In our study, a moderate concordance was observed between IPAQ and accelerometry in the assessment of PA in patients with PsA. IPAQ has shown reasonable agreement with accelerometry in other settings, such as with healthy adults (46), RA patients (8), and patients with multiple sclerosis (47).

Multivariate analysis showed that patients with PsA with higher disease activity, whether reflected by the DAS28 or DAPSA,

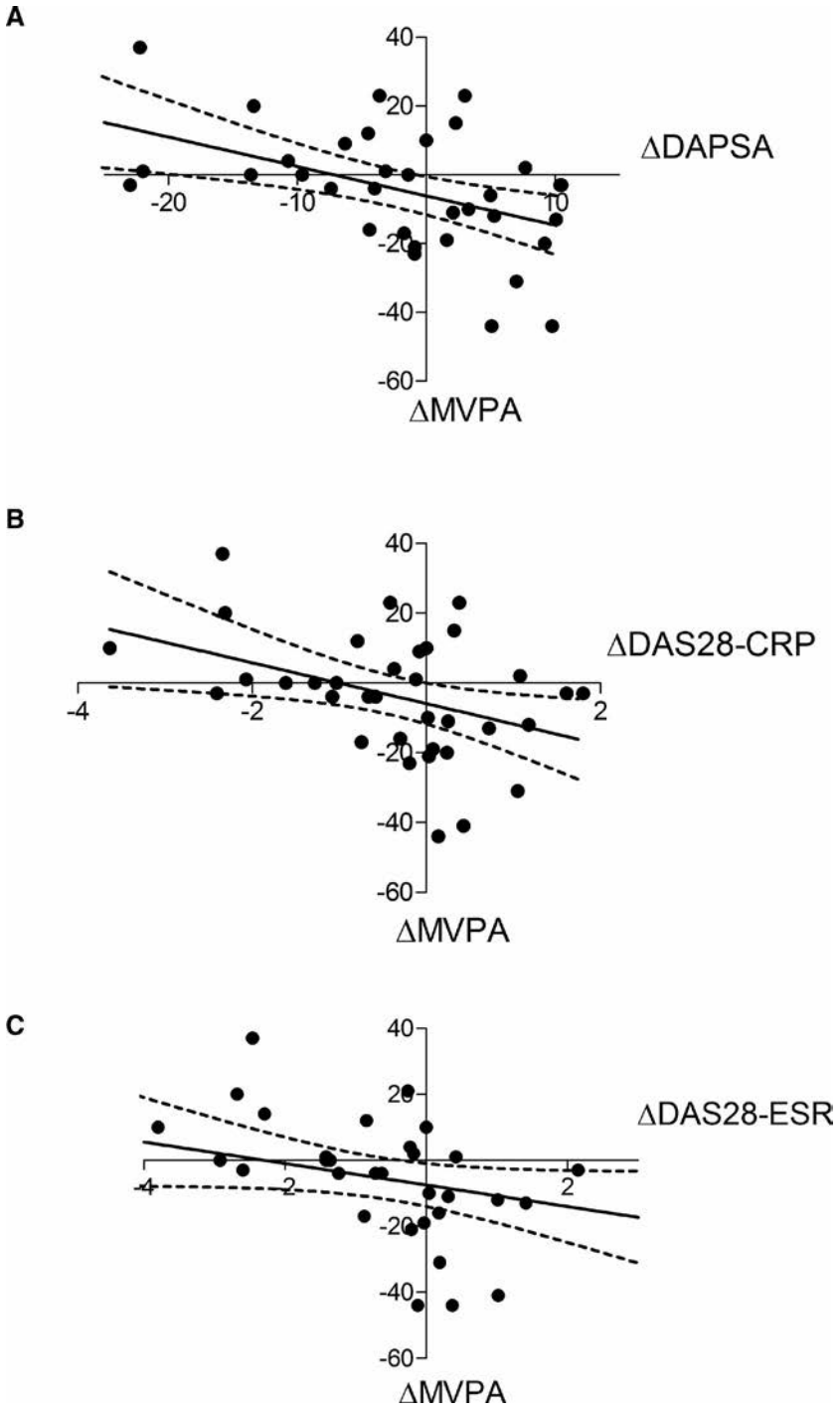

Figure 2. Correlation between variations in disease activity and physical activity in patients with psoriatic arthritis (PsA). Pearson's correlation between variations in disease activity as assessed by **A**, Disease Activity Index for Psoriatic Arthritis (ΔDAPSA), **B**, 28-joint Disease Activity Score using the C-reactive protein level (ΔDAS28-CRP), and **C**, DAS28 using the erythrocyte sedimentation rate (ΔDAS28-ESR), and time spent engaged in moderate-to-vigorous physical activity (ΔMVPA) as determined by accelerometry in 2 consecutives measurements spaced 6 months apart in a group of 36 patients with PsA. The x-axis represents the variations in disease activity by the different indexes. The y-axis represents the variations in MVPA. There was a significant inverse correlation between variations in DAPSA and DAS28-CRP, with respect to variations in MVPA ($r = –0.49$, $P = 0.002$ and $r = –0.4$, $P = 0.017$, respectively). The correlation between variation in DAS20-ESR and variations in MVPA showed a nearly significant inverse relationship ($r = –0.32$, $P = 0.06$). Individual dots indicate patients, the solid line shows regression, and the dotted lines indicate error.

engaged in significantly less PA, as assessed both by the IPAQ and accelerometry. When a second determination of PA (time spent doing MVPA, as measured by accelerometry) and disease activity (by DAPSA and DAS28-CRP) was carried out 6 months later, the relationship between the variations of both parameters with respect to basal levels correlated inversely. In agreement with this

finding, previous studies in patients with RA indicate that PA levels (as measured by questionnaires or by accelerometry) have an inverse relationship with disease activity (as assessed by DAS28 or by the Simplified Disease Activity Index [SDAI]) (8,13,15,48). One of these studies involved RA patients lacking lower-extremity disease activity, which suggests that the state of inflammation influences patients' tendency to reduce their levels of PA (8). In these studies, accelerometry was sufficiently sensitive to detect PA changes related to disease activity both in RA patients, who showed clinical improvements in response to treatment (13), and in patients who experienced a disease flare (8). Our data suggest that disease activity negatively impacts the PA capacity of patients with PsA.

The main limitation of this study is that its design may support the interpretation that insufficient PA may be responsible for increased disease activity in patients with PsA. However, the fact that patients with active disease tend to rest more, and conversely, that those with low disease activity benefit from PA, makes the validity of this alternative interpretation unlikely. Since patients were informed that their PA would be assessed, a possible selection bias of this study could be that patients with better physical ability would show a greater willingness to participate than those who were less physically fit. Another weakness of our study is that only 70% of the patients included in the initial visit came for the second evaluation.

Several disease activity indexes, such as the DAS, Clinical Disease Activity Index, SDAI, DAPSA, or American College of Rheumatology, allow physicians to quantify changes in the disease activity of RA or PsA over time. These indexes are liable to certain limitations related to both patient subjectivity and inter- and intraobserver variability (49). As our data indicated for patients with PsA and as stated above, by measuring variations in PA, accelerometry appears to be sufficiently sensitive to register changes in the clinical activity of PsA and RA (8,13). Consequently, accelerometry could be used as an objective and complementary method for assessing changes in disease activity variations.

An online survey conducted in 2013, involving >7,000 smartphone owners in the US, revealed that 79% of responders age 18–44 years have their phone on or near them for all but up to 2 hours of their waking day (50). For some time now, most smartphones available on the market have built-in accelerometer sensors. Although these devices have not yet been validated in patients with inflammatory joint diseases, implementation of this tool will allow physicians to better measure the real PA levels of rheumatic patients. As with patients with RA, because there seems to be an inverse relationship between PA levels and disease activity in PsA (8), the use of smartphones to assess PA could help rheumatologists not only to establish recommendations on cardiovascular risk, but also to make better treatment decisions for these patients.

In conclusion, we found that PA in patients with PsA is comparable with the general population, in terms of time spent in moderate-to-vigorous activity. PA, as assessed by accelerometry, appears to be sufficiently sensitive to detect changes in disease activity. However, this finding must be confirmed. We believe that the inclusion of PA assessments using accelerometry in randomized controlled trials could help to determine whether evaluation of PA will allow for more objective assessments of PsA disease activity.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Díaz-González had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Hernández-Hernández, Sánchez-Pérez, Luna-Gómez, Ferraz-Amaro, Díaz-González.

REFERENCES

1. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol 2012;2:1143–211.
2. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA 2009;301:2024–35.
3. Warren JM, Ekelund U, Besson H, Mezzani A, Geladas N, Vanhees L, et al. Assessment of physical activity. A review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil 2010; 17:127–39.
4. Van Poppel MN, Chinapaw MJ, Mokkink LB, van Mechelen W, Terwee CB. Physical activity questionnaires for adults: a systematic review of measurement properties. Sports Med 2010;40:565–600.
5. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35: 1381–95.
6. Aadland E, Ylvisaker E. Reliability of the Actigraph GT3X+ accelerometer in adults under free-living conditions. PLoS One 2015;10: e0134606.
7. Metsios GS, Stavropoulos-Kalinoglou A, Treharne GJ, Nevill AM, Sandoo A, Panoulas VF, et al. Disease activity and low physical activity associate with number of hospital admissions and length of hospitalisation in patients with rheumatoid arthritis. Arthritis Res Ther 2011;13:R108.
8. Hernandez-Hernandez V, Ferraz-Amaro I, Diaz-Gonzalez F. Influence of disease activity on the physical activity of rheumatoid arthritis patients. Rheumatology (Oxford) 2014;53:722–31.
9. Chen KY, Bassett DR Jr. The technology of accelerometry-based activity monitors: current and future. Med Sci Sports Exerc 2005;37: S490–500.
10. Bonomi AG, Goris AH, Yin B, Westerterp KR. Detection of type, duration, and intensity of physical activity using an accelerometer. Med Sci Sports Exerc 2009;41:1770–7.

11. Murphy SL, Smith DM, Clauw DJ, Alexander NB. The impact of momentary pain and fatigue on physical activity in women with osteoarthritis. Arthritis Rheum 2008;59:849–56.
12. Lee J, Song J, Hootman JM, Semanik PA, Chang RW, Sharma L, et al. Obesity and other modifiable factors for physical inactivity measured by accelerometer in adults with knee osteoarthritis. Arthritis Care Res (Hoboken) 2013;65:53–61.
13. Prioreschi A, Hodkinson B, Tikly M, McVeigh JA. Changes in physical activity measured by accelerometry following initiation of DMARD therapy in rheumatoid arthritis. Rheumatology (Oxford) 2014;53: 923–6.
14. Semanik P, Song J, Chang RW, Manheim L, Ainsworth B, Dunlop D. Assessing physical activity in persons with rheumatoid arthritis using accelerometry. Med Sci Sports Exerc 2010;42:1493–501.
15. Prioreschi A, Hodkinson B, Avidon I, Tikly M, McVeigh JA. The clinical utility of accelerometry in patients with rheumatoid arthritis. Rheumatology (Oxford) 2013;52:1721–7.
16. Legge A, Blanchard C, Hanly JG. Physical activity and sedentary behavior in patients with systemic lupus erythematosus and rheumatoid arthritis. Open Access Rheumatol 2017;9:191–200.
17. Eurenius E, Stenström CH, and the Para Study Group. Physical activity, physical fitness, and general health perception among individuals with rheumatoid arthritis. Arthritis Rheum 2005;53: 48–55.
18. Sokka T, Häkkinen A, Kautiainen H, Maillefert JF, Toloza S, Mørk Hansen T, et al. Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. Arthritis Rheum 2008;59:42–50.
19. Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJ, Nightingale P, Kitas GD, Koutedakis Y. Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. Ann Rheum Dis 2013;72:1819–25.
20. Tierney M, Fraser A, Kennedy N. Physical activity in rheumatoid arthritis: a systematic review. J Phys Act Health 2012;9:1036–48.
21. Lee S, Mendelsohn A, Sarnes E. The burden of psoriatic arthritis: a literature review from a global health systems perspective. P T 2010;35:680–9.
22. Thomsen RS, Nilsen TI, Haugeberg G, Bye A, Kavanaugh A, Hoff M. Impact of high-intensity interval training on disease activity and disease in patients with psoriatic arthritis: a randomized controlled trial. Arthritis Care Res (Hoboken) 2019;71:530–7.
23. Fongen C, Halvorsen S, Dagfinrud H. High disease activity is related to low levels of physical activity in patients with ankylosing spondylitis. Clin Rheumatol 2013;32:1719–25.
24. O'Dwyer T, O'Shea F, Wilson F. Physical activity in spondyloarthritis: a systematic review. Rheumatol Int 2015;35:393–404.
25. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.
26. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
27. Schoels MM, Aletaha D, Alasti F, Smolen JS. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. Ann Rheum Dis 2016;75:811–8.
28. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Clin Exp Rheumatol 2005;23:S93–9.
29. Smolen JS, Schoels M, Aletaha D. Disease activity and response assessment in psoriatic arthritis using the Disease Activity index for PSoriatic Arthritis (DAPSA): a brief review. Clin Exp Rheumatol 2015;33:S48–50.
30. Pincus T, Swearingen C, Wolfe F. Toward a multidimensional Health Assessment Questionnaire (MDHAQ): assessment of advanced activities of daily living and psychological status in the patient-friendly health assessment questionnaire format. Arthritis Rheum 1999;42:2220–30.
31. Chandran V, Bhella S, Schentag C, Gladman DD. Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. Ann Rheum Dis 2007;66:936–9.
32. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008;40:181–8.
33. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc 1998;30:777–81.
34. Roger-Silva D, Natour J, Moreira E, Jennings F. A resistance exercise program improves functional capacity of patients with psoriatic arthritis: a randomized controlled trial. Clin Rheumatol 2018;37:389–95.
35. Thomsen RS, Nilsen TIL, Haugeberg G, Bye A, Kavanaugh A, Hoff M. Effect of high-intensity interval training on cardiovascular disease risk factors and body composition in psoriatic arthritis: a randomised controlled trial. RMD Open 2018;4:e000729.
36. Haglund E, Bergman S, Petersson IF, Jacobsson LT, Strömbeck B, Bremander A. Differences in physical activity patterns in patients with spondylarthritis. Arthritis Care Res (Hoboken) 2012;64:1886–94.
37. Anthony Rodgers PV, Thomson Prentice, Tessa Tan-Torres Edejer, David Evans and Julia Lowe. The world health report 2002: reducing risks, promoting health. 2002. https://www.who.int/whr/2002/whr_overview_eng.pdf.
38. Torres T, Alexandre JM, Mendonca D, Vasconcelos C, Silva BM, Selores M. Levels of physical activity in patients with severe psoriasis: a cross-sectional questionnaire study. Am J Clin Dermatol 2014;15:129–35.
39. Wilson PB. Moderate-to-vigorous physical activity in individuals with psoriasis: associations with body surface area and subjective disease severity. G Ital Dermatol Venereol 2013;148:485–92.
40. Leino M, Mustonen A, Mattila K, Koulu L, Tuominen R. Perceived impact of psoriasis on leisure-time activities. Eur J Dermatol 2014;24:224–8.
41. Qureshi AA, Choi HK, Setty AR, Curhan GC. Psoriasis and the risk of diabetes and hypertension: a prospective study of US female nurses. Arch Dermatol 2009;145:379–82.
42. Mallbris L, Granath F, Hamsten A, Stahle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. J Am Acad Dermatol 2006;54:614–21.
43. Demirel R, Genc A, Ucok K, Kacar SD, Ozuguz P, Toktas M, et al. Do patients with mild to moderate psoriasis really have a sedentary lifestyle? Int J Dermatol 2013;52:1129–34.
44. Grimm EK, Swartz AM, Hart T, Miller NE, Strath SJ. Comparison of the IPAQ-Short Form and accelerometry predictions of physical activity in older adults. J Aging Phys Act 2012;20:64–79.
45. Fillipas S, Cicuttini F, Holland AE, Cherry CL. The international physical activity questionnaire overestimates moderate and vigorous physical activity in HIV-infected individuals compared with accelerometry. J Assoc Nurses AIDS Care 2010;21:173–81.
46. Hansen AW, Dahl-Petersen I, Helge JW, Brage S, Gronbaek M, Flensborg-Madsen T. Validation of an internet-based long version of the International Physical Activity Questionnaire in Danish adults using combined accelerometry and heart rate monitoring. J Phys Act Health 2014;11:654–64.
47. Weikert M, Motl RW, Suh Y, McAuley E, Wynn D. Accelerometry in persons with multiple sclerosis: measurement of physical activity or walking mobility? J Neurol Sci 2010;290:6–11.

48. Henchoz Y, Bastardot F, Guessous I, Theler JM, Dudler J, Vollenweider P, et al. Physical activity and energy expenditure in rheumatoid arthritis patients and matched controls. Rheumatology (Oxford) 2012;51:1500–7.
49. Marhadour T, Jousse-Joulin S, Chales G, Grange L, Hacquard C, Loeuille D, et al. Reproducibility of joint swelling assessments in long-lasting rheumatoid arthritis: influence on Disease Activity Score-28 values (SEA-Repro study part I). J Rheumatol 2010;37: 932–7.
50. Always connected: how smartphones and social keep us engaged. 2013. URL: https://www.slideshare.net/ScottValentine1/always-connected-how-smartphone-owners-stay-engaged.

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Factors Influencing Patient Decision-Making Concerning Treatment Escalation in Raynaud's Phenomenon Secondary to Systemic Sclerosis

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Objective. To explore patient priorities and ranking of factors influencing patient decision-making concerning treatment escalation in the management of Raynaud's phenomenon (RP) secondary to systemic sclerosis (SSc).

Methods. Patients with SSc were invited to participate in an online survey disseminated through patient-led organizations and social media platforms.

Results. Responses from 747 individuals with self-reported SSc-RP were evaluable with broad international representation. The mean ± SD age (54.7 ± 12.1 years), clinical phenotype, and disease subsets distribution (limited cutaneous SSc [402 of 747, 53.8%], diffuse cutaneous SSc [260 of 747, 34.8%], and overlap disease [85 of 747, 11.4%]) were consistent with expected demographic information. Around one-half (56.3%) of patients reported that their SSc-RP symptoms were adequately controlled. The 5 highest ranked factors (of 13) that would prompt treatment escalation for SSc-RP were as follows: 1) inability to use the fingers properly; 2) emergence of new digital ulcer on ≥1 fingers; 3) worsening pain or discomfort from RP; 4) more severe attacks; and 5) if it may help with internal problems. Despite symptoms not being adequately controlled, 47.1% were concerned about potential treatment side effects and were more likely to accept mild (~20–40%) versus severe (2%) side effects. Patients were open to different management strategies for uncontrolled RP that included adding new treatment in combination with existing treatment (52.8%), drug substitution (40.9%), increasing the current dose (28.8%), or focusing on nonpharmacologic approaches (29.7%).

Conclusion. We have identified the relative importance of different factors influencing patient preferences for treatment decision-making regarding SSc-RP. Side-effect profiles influence acceptability of drug treatments, and many patients report a preference for nonpharmacologic management of SSc-RP.

INTRODUCTION

Raynaud's phenomenon (RP) is responsible for significant pain and disability in patients with systemic sclerosis (SSc), despite the availability of a wide range of drug therapies (1,2). Furthermore, in SSc, digital vasospasm can be complicated by irreversible tissue ischemia including digital ulcers and gangrene. In addition, generalized vascular disease (vasculopathy) is a cardinal feature of SSc including visceral-based complications (e.g., pulmonary hypertension) (3). A unified vascular phenotype has been proposed in which vascular-acting therapies could be judiciously deployed as disease-modifying agents before the onset of irreversible tissue fibrosis and organ dysfunction (4).

In the absence of a validated instrument for objectively assessing SSc-RP activity/severity, the decision to both initiate and assess treatment for RP is usually based on clinician–patient discussions about symptom severity, drug tolerability, and the perceived effectiveness of existing/planned interventions (5). Treatment is given on a regular basis because patients, including those with SSc, have a limited ability to predict both the occurrence and severity of attacks of RP (2).

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SIGNIFICANCE & INNOVATIONS

- Hand function, physical symptoms, and preventing digital/internal complications influence patient decision-making in the management of systemic sclerosis (SSc)–Raynaud's phenomenon (RP).
- Side effects significantly impact on acceptability of drug treatment for SSc-RP.
- Pharmacologic and nonpharmacologic approaches toward treatment escalation should be adopted for suboptimally controlled SSc-RP.

Expert treatment recommendations for SSc-RP have been produced under the auspices of the British Society of Rheumatology, the European Alliance of Associations for Rheumatology, the UK Scleroderma Study Group, and the Scleroderma Clinical Trials Consortium/Canadian Scleroderma Research Group (6–9). In general, these have detailed the positioning of particular drug therapies but not practically how to either initiate and/or escalate drug therapies in clinical practice, including dosing strategies that could optimize drug tolerability, treatment adherence, and treatment efficacy. For example, higher (compared to lower) doses of calcium-channel blockers have been reported to be relatively more efficacious (10).

Treatment escalation via a treat-to-target approach has revolutionized the treatment of rheumatoid and other inflammatory arthritides and is widely used across medicine (e.g., in patients with hypertension and diabetes mellitus) (11–13). However, despite the availability of a wide range of drug therapies for RP, there is no evidence base to guide the optimal initiation and/or dose escalation, including failure after treatment, nor are the merits of different treatment approaches (e.g., initial combination versus goal-directed sequential monotherapy) considered. In addition, combination therapy is now considered the standard of care for the treatment of pulmonary hypertension, including in patients with SSc (14,15). Furthermore, little is known about the factors perceived by patients to be important in treatment escalation decision-making for SSc-RP.

Against this background, the primary aims of the current study were to explore patient priorities and ranking of factors influencing patient decision-making concerning treatment escalation in the management of SSc-RP. We also examined patient preferences regarding potential treatment strategies and acceptability of treatment side effects during treatment escalation for SSc-RP. A secondary objective was to explore whether differences existed across SSc disease subsets: diffuse and limited cutaneous SSc (dcSSc and lcSSc, respectively) and overlap SSc.

PATIENTS AND METHODS

Study design. Data were obtained from the Patient Survey of Experiences of Raynaud's Phenomenon (PASRAP) survey, the design of which has been previously described (16). In summary, the PASRAP was an international survey that sought to explore the multifaceted patient experience of RP, including approach to treatment. The link to the survey was widely distributed, including through social media (e.g., Facebook and Twitter), a scleroderma self-management website, and patient-led organizations (e.g., Scleroderma and Raynaud's UK and the Scleroderma Foundation). The survey consisted of a series of questions that included basic patient demographic and disease-related information, the impact and severity of RP and current treatments, the reasons to change current treatment and management strategies, and willingness to experience side effects. The survey questions are available online (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24710/abstract). Participants (≥18 years of age) were invited to complete the PASRAP if they had clinician-diagnosed RP and were asked to indicate their underlying diagnosis (e.g., SSc). The study was approved by the University of Michigan Institutional Review Board with exempt status (study ID: HUM00175143; OHRP IRB registration number: IRB00000246).

Statistical analysis. Demographic and baseline data, including age, sex, country, disease durations, history of diseases, medication, and treatment-related questions, were populated by scleroderma groups. Mean and SDs were reported for continuous variables; counts and percentages were reported for categorical variables. When comparing SSc groups, we performed an analysis of variance test for continuous variables that followed normal distribution, the Kruskal-Wallis test for continuous variables that did not follow normal distribution, and a chi-square test or Fisher's exact test for categorical variables. Percent of weight was calculated for different factors as follows: 1) for 13 factors in starting new treatment, assign first selected to last selected with scores 13 to 1 (i.e., assign scores in descending order) for each participant; 2) get sum of the scores for each of the reasons as numerator; 3) multiply number in the population by 13 as denominator; and 4) divide numerator (obtained weight) by denominator (sum weight) to get percent of weight (% weight).

RESULTS

Patient demographic information. The PASRAP was completed by 1,718 respondents between April 2020 and May 2020, of which 747 self-reported that their RP was secondary to SSc. Patient demographic information and disease and treatment characteristics are presented in Table 1, including for patients with lcSSc (54%), dcSSc (35%), and overlap SSc (11%). Patients' mean ± SD age was 54.7 ± 12.1 years, and the majority (93.5%) were female. More than one-half of patients reported living in the US (58.9%), and there was broad international representation including the UK (14.5%), Europe, and Australia. Patients were asked to identify when they first developed RP and were diagnosed with any underlying condition (e.g., SSc). Patient-reported median (interquartile range) disease duration for RP and SSc were 12 (5–24) and 7.0 (3.0–15.0) years, respectively.

Table 1. Patient demographic information including disease and treatment characteristics*

Characteristic	All SSc (n = 747)	LcSSc (n = 402)	DcSSc (n = 260)	Overlap SSc (n = 85)	*P*
Age, mean ± SD years (n = 747)	54.7 ± 12.1	55.2 ± 12.0	54.3 ± 12.0	53.2 ± 12.8	0.331
18–34	43 (5.8)	21 (5.2)	15 (5.8)	7 (8.2)	0.690
35–49	207 (27.7)	108 (26.9)	72 (27.7)	27 (31.8)	–
50–64	327 (43.8)	174 (43.3)	120 (46.2)	33 (38.8)	–
≥65	170 (22.8)	99 (24.6)	53 (20.4)	18 (21.2)	–
Sex (n = 744)					
Male	48 (6.5)	14 (3.5)	29 (11.2)	5 (6.0)	<0.001
Female	696 (93.5)	386 (96.5)	231 (88.8)	79 (94.0)	
Country (n = 747)					
Australia	34 (4.6)	22 (5.5)	9 (3.5)	3 (3.5)	0.069
Canada	26 (3.5)	12 (3.0)	11 (4.2)	3 (3.5)	–
Norway	21 (2.8)	13 (3.2)	6 (2.3)	2 (2.4)	–
UK	108 (14.5)	71 (17.7)	27 (10.4)	10 (11.8)	–
US	440 (58.9)	233 (58.0)	161 (61.9)	46 (54.1)	–
Other	118 (15.8)	51 (12.7)	46 (17.7)	21 (24.7)	–
Disease duration, median (IQR) years (n = 746)	7.0 (3.0–15.0)	8.0 (3.0–16.0)	6.0 (2.0–12.0)	9.0 (3.5–17.0)	0.014
RP duration, median (IQR) years (n = 746)	12.0 (5.0–24.0)	14.0 (6.0–27.0)	9.0 (4.0–18.0)	12.5 (6.0–28.5)	<0.001
History of DUs (n = 731)	284 (38.9)	148 (37.2)	112 (44.6)	24 (29.3)	0.028
Past gangrene (n = 284)	57 (20.1)	31 (20.9)	20 (17.9)	6 (25.0)	0.678
PAH (n = 731)	79 (10.8)	43 (10.8)	25 (10.0)	11 (13.4)	0.682
Calcium-channel blockers (n = 729)	295 (40.5)	157 (39.4)	102 (40.8)	36 (44.4)	0.699
Phosphodiesterase type 5 inhibitor (n = 729)	155 (21.3)	85 (21.4)	55 (22.0)	15 (18.5)	0.800
Endothelin receptor antagonists (n = 729)	32 (4.4)	21 (5.3)	10 (4.0)	1 (1.2)	0.252
Prostanoids (n = 729)	26 (3.6)	14 (3.5)	6 (2.4)	6 (7.4)	0.107
ACE inhibitor or angiotensin receptor (n = 729)	122 (16.7)	64 (16.1)	47 (18.8)	11 (13.6)	0.481
Fluoxetine (n = 729)	105 (14.4)	61 (15.3)	33 (13.2)	11 (13.6)	0.736

* Values are the number (%) unless indicated otherwise. ACE = angiotensin-converting enzyme; dcSSc = diffuse cutaneous systemic sclerosis; DU = digital ulcer; IQR = interquartile range; lcSSc = limited cutaneous systemic sclerosis; PAH = pulmonary arterial hypertension; RP = Raynaud's phenomenon; SSc = systemic sclerosis.

Consistent with expected prevalence of disease manifestations, there was a significant burden of digital vasculopathy, including history of ulcers (38.9%), past gangrene (20.1%), and pulmonary arterial hypertension (10.8%). Approximately one-half (40.5%) of patients were currently prescribed treatment with calcium-channel blockers. Respondents also reported treatment with phosphodiesterase type 5 inhibitors (21.3%), angiotensin-converting enzyme inhibitor, and/or angiotensin receptor blocker (16.7%) or fluoxetine (14.4%). A minority of patients were prescribed vasoactive treatment with either endothelin receptor antagonists (4.4%) or prostanoids (3.6%). Treatments for SSc-RP were similar across disease subsets (Table 1).

Impact of RP and treatment. Patients were asked to indicate on ordinal scale their level of satisfaction with their current medications in relieving their RP symptoms (very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, and very dissatisfied). Only one-half (56.3%) of

Table 2. Perceived impact of current systemic sclerosis (SSc)–Raynaud's phenomenon (RP) treatment*

	All SSc	LcSSc	DcSSc	Overlap SSc	*P*
Are your RP symptoms being adequately controlled? (n = 739)	416 (56.3)	222 (55.5)	147 (57.6)	47 (56.0)	0.862
How satisfied are you that your current medications are relieving your RP symptoms? (n = 739)					
Very satisfied	101 (13.7)	54 (13.5)	31 (12.2)	16 (19.0)	0.584
Somewhat satisfied	228 (30.9)	121 (30.3)	80 (31.4)	27 (32.1)	–
Neither satisfied nor dissatisfied	253 (34.2)	139 (34.8)	87 (34.1)	27 (32.1)	–
Somewhat dissatisfied	77 (10.4)	41 (10.3)	32 (12.5)	4 (4.8)	–
Very dissatisfied	80 (10.8)	45 (11.3)	25 (9.8)	10 (11.9)	–

* Values are the number (%) unless indicated otherwise. DcSSc = diffuse cutaneous systemic sclerosis; lcSSc = limited cutaneous systemic sclerosis.

Table 3. Reasons that would make patients (n = 718) with systemic sclerosis (SSc) consider starting a new treatment for Raynaud's phenomenon (RP)*

	All SSc	LcSSc	DcSSc	Overlap SSc	*P*
Hand function					
Inability to use fingers properly due to RP	502 (69.9)	276 (70.4)	174 (69.9)	52 (67.5)	0.881
Physical symptoms					
Worsening pain or discomfort from RP	461 (64.2)	257 (65.6)	161 (64.7)	43 (55.8)	0.262
More severe attacks	392 (54.6)	218 (55.6)	136 (54.6)	38 (49.4)	0.601
More frequent attacks	316 (44.0)	175 (44.6)	109 (43.8)	32 (41.6)	0.879
Worsening numbness from RP	278 (38.7)	156 (39.8)	100 (40.2)	22 (28.6)	0.153
Longer attacks	252 (35.1)	137 (34.9)	92 (36.9)	23 (29.9)	0.522
Fingers feeling colder	201 (28.0)	107 (27.3)	71 (28.5)	23 (29.9)	0.876
Worsening digital color changes from RP	189 (26.3)	98 (25.0)	74 (29.7)	17 (22.1)	0.280
Prevention of complications					
Develop an ulcer on ≥1 fingers	465 (64.8)	270 (68.9)	153 (61.4)	42 (54.5)	0.022
If it may help with internal organ problems	364 (50.7)	208 (53.1)	122 (49.0)	34 (44.2)	0.289
Develop new telangiectasia on fingers	146 (20.3)	82 (20.9)	56 (22.5)	8 (10.4)	0.064
Emotional impact					
Emotion effect of RP including annoyance, anger, frustration, and anxiety	173 (24.1)	91 (23.2)	67 (26.9)	15 (19.5)	0.343
Embarrassment and/or dissatisfaction with the appearance of fingers during attacks	100 (13.9)	45 (11.5)	42 (16.9)	13 (16.9)	0.116

* Values are the number (%) unless indicated otherwise. Grouping of items is based on previous qualitative research exploring the patient experience of RP (16,17). DcSSc = diffuse cutaneous systemic sclerosis; lcSSc = limited cutaneous systemic sclerosis.

patients were satisfied that their RP symptoms were being adequately controlled. The perceived impact of current RP treatment is presented in Table 2. Patients were most likely to be either neither satisfied nor dissatisfied (34.2%) or somewhat satisfied (30.9%). Ten percent of patients were either very dissatisfied (10.8%) or somewhat dissatisfied (10.4%).

Reasons and relative ranking for starting a new RP treatment. Patients were asked to indicate all the reasons (of 13) that would make them consider starting a new treatment for RP (Table 3). The 5 highest ranked (Figure 1) reasons were as follows: 1) inability to use the fingers properly due to RP; 2) if they developed an ulcer on ≥1 fingers; 3) worsening pain or discomfort of RP; 4) more severe attacks; and 5) if it may help with internal problems.

Willingness to experience side effects. Patients were asked about their willingness to experience side effects if a treatment was effective for RP (Table 4). Patients were much more likely to accept minor versus severe side effects: headache (39.8% versus 2.1%), nausea (22.1% versus 2.1%), and light-headedness (28.1% versus 1.9%). Almost one-half (47.1%) of patients indicated that they would not be willing to experience any side effects from treatment.

Management strategies for RP. Patients were asked which management approaches they would consider if their RP symptoms were poorly controlled (Table 5). Approximately one-half of patients would either consider adding a new treatment to existing drug treatment (52.8%) or stopping existing treatment and starting a new treatment (40.9%). Approximately one-third of patients would either increase the dose of existing drug treatment (28.8%) or concentrate on non-drug approaches (29.7%).

Differences between SSc disease subsets. There was no significant difference in the impact or perceived benefit of current treatment for SSc-RP between disease subsets (Table 2). Patients with lcSSc ranked digital ulcers as the highest reason to change treatment for RP (Table 3). There were subtle differences in the lowest ranking reasons between disease subsets (Figure 1). There was no difference between SSc subsets in willingness to experience side effects (Table 4) or management approaches (Table 5).

DISCUSSION

To our knowledge, this is the first study to examine patients' beliefs and preferences about treatment escalation for SSc-RP, and it provides a number of novel insights that could be used to inform future treatment strategy guidelines. Our study highlights the potential reasons and relative ranking (importance) that would make patients consider starting a new treatment for RP. Inability to use the fingers properly due to RP was the highest ranking reason to start a new treatment for RP. Physical symptoms including pain and the severity of attacks of RP were considered central features of the lived patient experience of RP (17). Patients strongly indicated that treatment for RP should also seek to positively modify digital ulcer (ranked second) and internal organ-based (ranked fifth) complications of the disease. Although RP is associated with broad emotional impact including fear, anxiety, embarrassment, and dissatisfaction, such aspects were considered (relatively) to be less important drivers to change treatment.

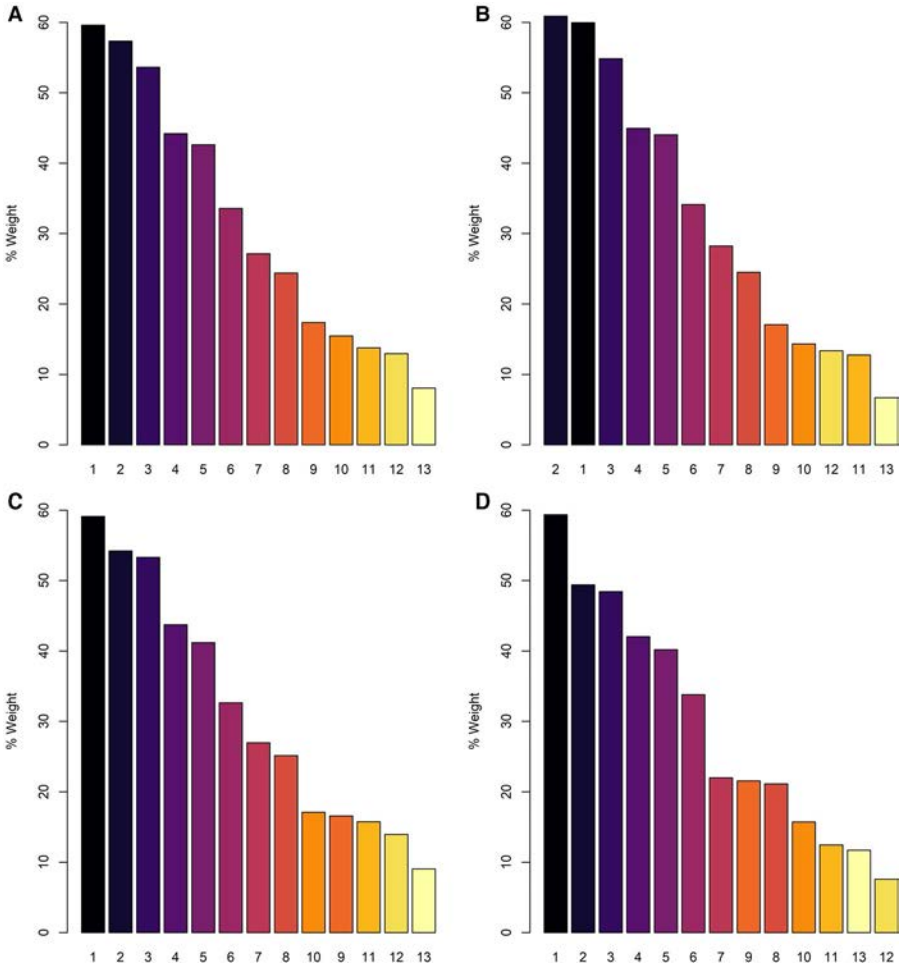

Figure 1. Ranked reasons why patients with systemic sclerosis (SSc) would consider starting a new treatment for Raynaud's phenomenon (RP) for all patients with SSc (**A**), those with limited cutaneous SSc (lcSSc) (**B**), those with diffuse cutaneous SSc (dcSSc) (**C**), and those with overlap SSc (**D**). 1 = inability to use fingers properly due to RP; 2 = develop an ulcer on ≥1 fingers; 3 = worsening pain or discomfort from RP; 4 = more severe attacks; 5 = if it may help with internal organ problems; 6 = more frequent attacks; 7 = worsening numbness from RP; 8 = longer attacks; 9 = fingers feeling colder; 10 = worsening digital color changes from RP; 11 = emotion effect from RP including annoyance, anger, frustration, and anxiety; 12 = develop new telangiectasia on fingers; 13 = embarrassment and/or dissatisfaction with the appearance of fingers during attacks.

Our data also further benchmark the lived burden of RP in patients with SSc and the need for effective treatments. Only one-half of patients reported that their RP symptoms were being adequately controlled. However, there is evidence of clear discordance between patients' expectations about the goals of treatment against their willingness to experience side effects. For example, approximately one-half of patients indicated that they would not be willing to accept any side effects with an effective treatment for RP. Furthermore, the magnitude (or severity) of side effects is considered to be of major importance to patients with SSc-RP.

Table 4. Patients' (n = 701) willingness to experience side effects if a treatment was effective for systemic sclerosis (SSc)–Raynaud's phenomenon*

	All SSc	LcSSc	DcSSc	Overlap SSc	*P*
Mild headache	279 (39.8)	146 (38.2)	100 (41.7)	33 (41.8)	0.654
Severe headache	15 (2.1)	10 (2.6)	4 (1.7)	1 (1.3)	0.618
Mild nausea	155 (22.1)	80 (20.9)	54 (22.5)	21 (26.6)	0.538
Severe nausea	15 (2.1)	10 (2.6)	5 (2.1)	0 (0.0)	0.342
Mild light-headedness	197 (28.1)	117 (30.6)	65 (27.1)	15 (19.0)	0.101
Severe light-headedness	13 (1.9)	10 (2.6)	3 (1.3)	0 (0.0)	0.275
None	330 (47.1)	183 (47.9)	109 (45.4)	38 (48.1)	0.817

* Values are the number (%) unless indicated otherwise. DcSSc = diffuse cutaneous systemic sclerosis; lcSSc = limited cutaneous systemic sclerosis.

Table 5. Management approaches that patients (n = 701) with systemic sclerosis (SSc) would consider if their Raynaud's phenomenon symptoms were poorly controlled*

	All SSc	LcSSc	DcSSc	Overlap SSc	*P*
Add a new treatment to existing drug treatment	370 (52.8)	194 (50.8)	135 (56.3)	41 (51.9)	0.408
Increase the dose of existing drug treatment	202 (28.8)	120 (31.4)	66 (27.5)	16 (20.3)	0.118
Stop existing treatment and start a new treatment	287 (40.9)	146 (38.2)	109 (45.4)	32 (40.5)	0.206
Focus on non-drug approaches	208 (29.7)	122 (31.9)	62 (25.8)	24 (30.4)	0.265

* Values are the number (%) unless indicated otherwise. DcSSc = diffuse cutaneous systemic sclerosis; lcSSc = limited cutaneous systemic sclerosis.

Patients were much more likely to be willing to experience minor (~20–40%) compared to severe (~2%) side effects (headache, nausea, and light-headedness).

Other novel findings were the lack of any impact of disease subsets on existing RP treatments and priorities for treatment escalation. However, patients with lcSSc indicated that the highest ranking reason to change treatment was for digital ulcer disease. Furthermore, there were some subtle changes in the ranking of the lowest ranking reasons between disease subsets. Irrespective of disease subset, there was significant unwillingness to accept side effects for an effective treatment for RP.

A key practical consideration relates to the paucity of existing evidence to inform management after treatment failure. Approximately one-half of patients would either consider substituting (52.8%) or adding in combination (40.9%) new drug therapy for RP, and one-third (28.8%) would increase the dose of current treatment. This is of interest because experts from the Scleroderma Clinical Trials Consortium and the Canadian Scleroderma Research Group, in general, propose an additive approach (with drugs used in combination) for the treatment of SSc-RP (9). One-third (29.7%) of patients also indicated that they are keen to consider nonpharmacologic approaches to management, although the evidence base to support these interventions at present are limited (18).

There was significant heterogeneity and ranking (of importance) of the reasons why patients would consider changing current treatment. SSc-RP clinical trials have previously focused on the frequency and duration of SSc-RP attacks as the primary trial end points. Intriguingly, in our study, attack frequency/duration was not prioritized by patients as factors that would lead them to consider treatment escalation. We observed impaired hand function (i.e., inability to use the hands properly due to RP) as the highest ranked factor that might prompt change of treatment. The Raynaud's Condition Score (RCS) is a validated outcome measure that assesses the level of difficultly due to RP and captures broader aspects of the patient experience including digital ulcers and numbness (19,20). However, concerns have been raised by experts in SSc-RP about the limitations of the RCS diary, which might impede on drug development programs (21). Ongoing collaborative international research is seeking to develop novel patient-reported outcome measures to assess the multifaceted impact and severity of digital vasculopathy in SSc, including RP (17,22–24). Future research should also examine noninvasive microvascular (e.g., structural and function) imaging to assess the impact of treatment on microangiopathy in SSc, in particular, in early phase studies of SSc-RP.

Consensus must be achieved with relevant stakeholders, including patients, about whether treatment escalation for SSc-RP should also seek to positively modify digital ulcer disease (occurrence and healing) and/or systemic vasculopathic complications. Another important aspect related to treatment must explore the concept of discrete attacks of RP. For example, in our previous study using the PASRAP, only 2% of patients (with primary and secondary RP) defined RP using the word 'attack' (16). Indeed, many patients with SSc have symptoms throughout the year, and it is uncertain whether relatively asymptomatic color change necessarily warrants treatment. Another major issue would likely relate to the impact of seasonal variation in environmental temperature and behavioral factors because these are associated with greater severity of SSc-RP (25,26). Patients with RP are increasingly using internet-based information to learn more about their condition, including approaches to treatment; however, the overall quality and readability is poor (26,27). Therefore, there is a need to develop disease-specific and accessible information to inform patient decision-making for SSc-RP (27,28).

A major strength of our study was the large number (~750) of patients with SSc who participated in the study. Another key strength is that missing responses were generally uncommon. Our survey population was based on anonymously self-reported information from patients with SSc and therefore was not amenable to confirmatory chart review, including diagnosis, subset, symptoms, and complications. However, the patient demographic information, clinical phenotype, and disease subsetting suggest that our cohort was representative of SSc based on previous registry analyses. For example, pulmonary arterial hypertension was reported to be present in ~10% of patients (29,30) and past digital ulcers in ~40% (approximately one-half of patients with SSc report a history of ulcers) (4,31,32). Past gangrene was reported by ~20–25% of patients, which is higher than previously reported. For example, in a study from the European Scleroderma Trials and Research Group database, which included 1,757 patients, 8.9% had current or previous digital gangrene (33). In our study, patients were

only asked about gangrene if they indicated that they had previously developed digital ulcers. Therefore, it could be expected that gangrene would be more common/overrepresented in patients with SSc and established digital vasculopathy (i.e., history of ulcers). Calcium-channel blockers were the most commonly indicated drug therapy, followed by phosphodiesterase type 5 inhibitors, which reflects current clinical practice (7,9). Although we prespecified the 13 reasons why patients may change treatment for RP, our previous qualitative research, including a recent study from the PASRAP, supports the choice of these reasons, including how patients define their RP (16,17).

In conclusion, our study provides a number of novel insights into patient's beliefs and preferences about treatment escalation for SSc-RP. These include the reasons (and relative ranking) why patients would change their current treatment and possible therapeutic strategies. Side effects significantly impact on acceptability of drug treatment for SSc-RP. Future research is required to optimize treatment for SSc-RP, including the need for decision analysis to help patients determine their preferences for management and to establish consensus as to whether such an approach should also seek to modify SSc-related digital and/or systemic vasculopathy.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Hughes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hughes, Huang, Pauling, Sabbagh, Khanna.

Acquisition of data. Hughes, Huang, Pauling, Sabbagh, Khanna.

Analysis and interpretation of data. Hughes, Huang, Pauling, Sabbagh, Khanna.

REFERENCES

1. Bassel M, Hudson M, Taillefer SS, Schieir O, Baron M, Thombs BD. Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian National Survey. Rheumatology (Oxford) 2011;50:762–7.
2. Hughes M, Snapir A, Wilkinson J, Snapir D, Wigley FM, Herrick AL. Prediction and impact of attacks of Raynaud's phenomenon, as judged by patient perception. Rheumatology (Oxford) 2015;54:1443–7.
3. Matucci-Cerinic M, Kahaleh B, Wigley FM. Evidence that systemic sclerosis is a vascular disease [review]. Arthritis Rheum 2013;65:1953–62.
4. Hughes M, Allanore Y, Chung L, Pauling JD, Denton CP, Matucci-Cerinic M. Raynaud phenomenon and digital ulcers in systemic sclerosis. Nat Rev Rheumatol 2020;16:208–21.
5. Hughes M, Khanna DK, Pauling JD. Drug Initiation and escalation strategies of vasodilator therapies for Raynaud's phenomenon: can we treat to target? Rheumatology (Oxford) 2020;59:464–6.
6. Meier FM, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2012;71:1355–60.
7. Hughes M, Ong VH, Anderson ME, Hall F, Moinzadeh P, Griffiths B, et al. Consensus best practice pathway of the UK Scleroderma Study Group: digital vasculopathy in systemic sclerosis. Rheumatology (Oxford) 2015;54:2015–24.
8. Denton C, Hughes M, Gak N, Vila J, Buch MH, Chakravarty K, et al. BSR and BHPR guideline for the treatment of systemic sclerosis. Rheumatology (Oxford) 2016;55:1906–10.
9. Fernández-Codina A, Walker KM, Pope JE, on behalf of the Scleroderma Algorithm Group. Treatment algorithms for systemic sclerosis according to experts. Arthritis Rheumatol 2018;70:1820–8.
10. Rirash F, Tingey PC, Harding SE, Maxwell LJ, Tanjong Ghogomu E, Wells GA, et al. Calcium channel blockers for primary and secondary Raynaud's phenomenon. Cochrane Database Syst Rev 2017;12:CD000467.
11. Atar D, Birkeland KI, Uhlig T. "Treat to target": moving targets from hypertension, hyperlipidaemia and diabetes to rheumatoid arthritis. Ann Rheum Dis 2010;69:629–30.
12. Solomon DH, Bitton A, Katz JN, Radner H, Brown EM, Fraenkel L. Treat to target in rheumatoid arthritis: fact, fiction, or hypothesis? [review]. Arthritis Rheumatol 2014;66:775–82.
13. Van Vollenhoven R. Treat-to-target in rheumatoid arthritis: are we there yet? Nat Rev Rheumatol 2019;15:180–6.
14. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373:834–44.
15. Lajoie AC, Bonnet S, Provencher S. Combination therapy in pulmonary arterial hypertension: recent accomplishments and future challenges. Pulm Circ 2017;7:312–25.
16. Murphy SL, Lescoat A, Alore M, Hughes M, Pauling JD, Sabbagh M, et al. How do patients define Raynaud's phenomenon? Differences between primary and secondary disease. Clin Rheumatol 2021;40:1611–6.
17. Pauling JD, Domsic RT, Saketkoo LA, Almeida C, Withey J, Jay H, et al. Multinational qualitative research study exploring the patient experience of Raynaud's phenomenon in systemic sclerosis. Arthritis Care Res (Hoboken) 2018;70:1373–84.
18. Daniels J, Pauling JD, Eccleston C. Behaviour change interventions for the management of Raynaud's phenomenon: a systematic literature review. BMJ Open 2018;8:e024528.
19. Merkel PA, Herlyn K, Martin RW, Anderson JJ, Mayes MD, Bell P, et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. Arthritis Rheum 2002;46:2410–20.
20. Khanna PP, Maranian P, Gregory J, Khanna D. The minimally important difference and patient acceptable symptom state for the Raynaud's condition score in patients with Raynaud's phenomenon in a large randomised controlled clinical trial. Ann Rheum Dis 2010;69:588–91.
21. Pauling JD, Frech TM, Hughes M, Gordon JK, Domsic RT, Anderson ME, et al. Patient-reported outcome instruments for assessing Raynaud's phenomenon in systemic sclerosis: a SCTC vascular working group report. J Scleroderma Relat Disord 2018;3:249–52.
22. Pauling JD, Saketkoo LA, Matucci-Cerinic M, Ingegnoli F, Khanna D. The patient experience of Raynaud's phenomenon in systemic sclerosis. Rheumatology (Oxford) 2019;58:18–26.
23. Hughes M, Pauling JD. Exploring the patient experience of digital ulcers in systemic sclerosis. Semin Arthritis Rheum 2019;48:888–94.
24. Hughes M, Pauling JD, Jones J, Denton CP, Domsic RT, Frech TM, et al. Multicenter qualitative study exploring the patient experience

of digital ulcers in systemic sclerosis. Arthritis Care Res (Hoboken) 2020;72:723–33.

25. Pauling JD, Reilly E, Smith T, Frech TM. Factors influencing Raynaud's condition score diary outcomes in systemic sclerosis. J Rheumatol 2019;46:1326–34.
26. Hughes M. Effect of season on internet searches for information on Raynaud phenomenon. J Rheumatol 2019;46:1543–4.
27. Devgire V, Martin AF, McKenzie L, Sandler RD, Hughes M. A systematic review of internet-based information for individuals with Raynaud's phenomenon and patients with systemic sclerosis. Clin Rheumatol 2020;39:2363–7.
28. Spierings J, van Rhijn-Brouwer FC, de Bresser CJ, Mosterman PT, Pieterse AH, Vonk MC, et al. Treatment decision-making in diffuse cutaneous systemic sclerosis: a patient's perspective. Rheumatology (Oxford) 2020;59:2052–61.
29. Avouac J, Airò P, Meune C, Beretta L, Dieude P, Caramaschi P, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol 2010;37:2290–8.
30. Vandecasteele E, Melsens K, Thevissen K, De Pauw M, Deschepper E, Decuman S, et al. Prevalence and incidence of pulmonary arterial hypertension: 10-year follow-up of an unselected systemic sclerosis cohort. J Scleroderma Relat Disord 2017;2:196–202.
31. Hughes M, Herrick AL. Digital ulcers in systemic sclerosis. Rheumatology (Oxford) 2017;56:14–25.
32. Morrisroe K, Stevens W, Sahhar J, Ngian GS, Ferdowsi N, Hill CL, et al. Digital ulcers in systemic sclerosis: their epidemiology, clinical characteristics, and associated clinical and economic burden. Arthritis Res Ther 2019;21:299.
33. Mihai C, Distler O, Gheorghiu AM, Constantin P, Dobrota R, Jordan S, et al. Incidence and risk factors for gangrene in patients with systemic sclerosis from the EUSTAR cohort. Rheumatology (Oxford) 2020;59:2016–23.

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BRIEF REPORT

Mortality Among Patients With Polymyalgia Rheumatica: A Retrospective Cohort Study

Richard Partington, Sara Muller, Christian D. Mallen, Alyshah Abdul Sultan, and Toby Helliwell

Objective. To determine whether a diagnosis of polymyalgia rheumatica (PMR) is associated with premature mortality.

Methods. We extracted anonymized electronic medical records of patients ages >40 years who were eligible for linkage with the Office for National Statistics Death Registration data set, from the Clinical Practice Research Datalink from 1990 to 2016. Patients with PMR were individually matched, by age, sex, and registered general practice, with up to 5 controls without PMR. The total number and proportion of deaths and mortality rates were calculated. The mortality rate ratio (MRR) with 95% confidence interval (95% CI), adjusted for age, sex, region, smoking status, body mass index, and alcohol consumption, was calculated using Poisson regression. The 20 most common causes of death were tabulated.

Results. A total of 18,943 patients with PMR were matched to 87,801 controls. The mean ± SD follow-up after date of diagnosis was 8.0 ± 4.4 years in patients with PMR and 7.9 ± 4.6 years in controls. PMR was not associated with an increase in the risk of death (adjusted MRR 1.00 [95% CI 0.97–1.03]) compared to matched controls. Causes of death were broadly similar between patients with PMR and controls, although patients with PMR were slightly more likely to have a vascular cause of death recorded (24% versus 23%).

Conclusion. A diagnosis of PMR does not appear to increase the risk of premature death. Minor variations in causes of death were observed, but overall this study is reassuring for patients with PMR and for clinicians.

INTRODUCTION

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic condition that predominantly affects older individuals (1) and can have a devastating impact on patients' lives. Classic symptoms of PMR include stiffness, pain, and impairment to daily activities (2). A recent study of PMR epidemiology estimated the incidence and prevalence of PMR to be 95.9 (95% confidence interval [95% CI] 94.9–96.8) per 100,000 person years and 0.85%, respectively (1).

A recent systematic review found that patients with PMR had a higher burden of comorbid disease when compared to age- and sex-matched controls (3). However, 3 previous studies reported no difference or reduced premature mortality among patients diagnosed with PMR (4–6).

Given the high burden of comorbid disease among patients with PMR, the raised systemic levels of inflammation associated with PMR, and the prolonged glucocorticoid (GC) therapy with which many patients with PMR are treated, it is important to ascertain whether a diagnosis of PMR is associated with an increased risk of premature mortality.

PATIENTS AND METHODS

Data source. The National Health Service (NHS) provides health care to all UK residents, and 98% of people in the UK are registered with a general practice. Approximately 90% of patient health care visits in the UK occur in primary care (7). We utilized data from the Clinical Practice Research Datalink (CPRD; version

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care. This study is based in part on data from the Clinical Practice Research Datalink GOLD database obtained under license from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the author(s) alone.

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- To the best of our knowledge, the present study is the largest study of mortality among patients with polymyalgia rheumatica, including over 100,000 patients and controls.
- A diagnosis of polymyalgia rheumatica does not increase the risk of premature death.
- The cause of death is similar among patients with polymyalgia rheumatica compared to controls.

July 2017), which contains data from 17 million contributing patients across 718 practices (7.5% of total patients). This database, containing electronic, coded information collected during the course of routine health care, is representative of the UK population in terms of age, sex, and ethnicity (8) and has been used extensively for research. This study was approved by the CPRD's Independent Scientific Advisory Committee (protocol number 17_203RA).

The CPRD can link to death registration data from the Office for National Statistics (ONS). Only practices based in England are eligible for linkage and, of those, 75% have consented (8). Where consent exists, patient level data is linked via NHS Digital to the other established data sources. The linkage between the CPRD and death registration data is available from January 1998 until February 2018. This data set also contains information on the official date of death, the date of registration of death, the underlying cause of death, and any other contributing factors given (9).

Definition of incident PMR. The exposed group was ages ≥40 years with a diagnosis of PMR as recorded in the CPRD. Each patient had a Read code diagnosis for PMR (N20 polymyalgia rheumatica; N200.00 giant cell arteritis with polymyalgia rheumatica) between February 1, 1998 and January 1, 2018 and 2 prescriptions for GCs, the first made within 6 months of PMR diagnosis, and the second within 6 months of the first diagnosis. This definition replicates previous CPRD studies of PMR (10) and provides supporting information as to the accuracy of the diagnosis. In addition to these requirements, each patient had at least 3 years of continuous follow-up prior to the date of PMR diagnosis (the index date).

Selection of unexposed group. Each individual with PMR was matched with up to 5 unexposed people. The matching criteria utilized included year of birth ± 3 years, sex, and registered practice. The index date for each exposed person was assigned

Table 1. Demographic information of included patients*

	Total	Exposed	Unexposed
Age, mean ± SD years	73.6 ± 8.9	73.8 ± 9.1	73.5 ± 8.9
Sex			
Male	34,559 (32.4)	6,273 (33.1)	28,286 (32.2)
Female	72,185 (67.6)	12,670 (66.9)	59,515 (67.8)
Region			
Northeast	1,740 (1.6)	306 (1.6)	1,434 (1.6)
Northwest	13,428 (12.6)	2,366 (12.5)	11,062 (12.6)
Yorkshire & the Humber	3,574 (3.4)	639 (3.4)	2,935 (3.3)
East Midlands	2,853 (2.7)	499 (2.6)	2,354 (2.7)
West Midlands	15,032 (14.1)	2,609 (13.8)	12,423 (14.1)
East of England	15,320 (14.4)	2,674 (14.1)	12,646 (14.4)
Southwest	17,137 (16.1)	3,042 (16.1)	14,095 (16.1)
South central	14,075 (13.2)	2,517 (13.3)	11,558 (13.2)
London	7,732 (7.2)	1,456 (7.7)	6,276 (7.1)
Southeast coast	15,853 (14.9)	2,835 (15.0)	13,018 (14.8)
BMI category			
Normal (18.5–24.9)	34,552 (32.4)	6,052 (31.9)	28,500 (32.5)
Underweight (<18.5)	1,986 (1.9)	0,221 (1.2)	1,765 (2)
Overweight (25–29.9)	36,515 (34.2)	6,923 (36.5)	29,592 (33.7)
Obese (≥30)	21,521 (20.2)	4,132 (21.8)	17,389 (19.8)
Missing	12,170 (11.4)	1,615 (8.5)	10,555 (12)
Smoking			
Nonsmoker	90,111 (84.4)	16,582 (87.5)	73,529 (83.8)
Smoker	11,823 (11.1)	1,827 (9.6)	9,996 (11.4)
Missing	4,810 (4.5)	0,534 (2.8)	4,276 (4.9)
Alcohol			
Never/no current	21,546 (20.2)	3,779 (19.9)	17,767 (20.2)
<10 units per week	55,927 (52.4)	10,369 (54.7)	45,558 (51.9)
≥10 units per week	16,133 (15.1)	2,942 (15.5)	13,191 (15)
Missing	13,138 (12.3)	1,853 (9.8)	11,285 (12.9)
Follow-up, mean ± SD years	7.9 ± 4.6	8.0 ± 4.4	7.9 ± 4.6

* Values are the number (%) unless indicated otherwise. BMI = body mass index.

Table 2. Number, proportion, and causes of death (in order of frequency) in patients with PMR (exposed group)*

	Exposed group
Total deaths	6,046 (31.9)
Rate per 1,000 patient-years (95% CI)	39.9 (38.9–41)
Mortality rate ratio (95% CI)†	1.00 (0.97–1.03)
Causes of death	
Chronic ischemic heart disease	464 (7.7)
Acute myocardial infarction	409 (6.8)
Chronic obstructive pulmonary disease	327 (5.4)
Malignant neoplasm, bronchus or lung	316 (5.2)
Bronchopneumonia	258 (4.3)
Pneumonia	243 (4.0)
Atherosclerotic heart disease	187 (3.1)
Vascular dementia	123 (2.0)
Urinary tract infection	115 (1.9)
Malignant neoplasm, pancreas	109 (1.8)
Cerebrovascular disease	108 (1.8)
Alzheimer's disease	106 (1.8)
Malignant neoplasm without specification	103 (1.7)
Malignant neoplasm, breast	99 (1.6)
Other interstitial pulmonary diseases	93 (1.5)
Congestive heart failure	84 (1.4)
Malignant neoplasm, colon	84 (1.4)
Aortic (valve) stenosis	71 (1.2)
Cerebral infarction	68 (1.1)
Malignant neoplasm, esophagus	67 (1.1)
Others	2,612 (43.8)

* Values are the number (%) unless indicated otherwise. 95% CI = 95% confidence interval; PMR = polymyalgia rheumatica.
† This value pertained to the ratio of the mortality rate among the exposed population divided by the mortality rate among the unexposed population.

to their matched unexposed group, for whom contributing data were also available since that date and for 3 years prior.

Study period. The start of the present study was defined as the index date, which was the date of PMR diagnosis for the exposed group and their matched group. Follow-up continued until the earliest of the following events: 1) January 1, 2018 (the end of the period encompassed by ONS death registration data), 2) the date when a patient transferred out of the practice, 3) the last date of data collection from the practice, or 4) the date of death.

Statistical analysis. Descriptive statistics were used to find the average age of the exposed and unexposed participants, as well as the proportion of exposed and unexposed participants per region, sex, smoking status, body mass index (BMI) category, alcohol consumption status, and follow-up prior to and following the index date. This analysis was conducted to ensure that the exposed and unexposed groups were similar.

The primary outcome measures were total number of deaths in exposed and unexposed groups and estimated mortality rate per 1,000 person-years (with 95% CIs). Estimates of survival were constructed using the Kaplan-Meier method. The ONS death registration data include the date of death, the date of death registration, and the cause of death. For this study, the date of death was used, and the cause of death was included as a secondary analysis variable.

A Poisson regression model was used to calculate the mortality rate ratio (MRR; 95% CI) to compare the mortality rate of patients with PMR to those without. This figure was adjusted for age, sex, region, smoking status, BMI category, and alcohol consumption. If data regarding covariates were missing, patients were assumed to be nonsmokers, consume no alcohol, and have a normal BMI.

RESULTS

A total of 18,943 patients with PMR and 87,801 matched unexposed individuals were included in the analysis. The demographic characteristics of patients are shown (Table 1). The average age at diagnosis, sex, and region of general practice were very similar between the exposed and unexposed groups. The mean age of the exposed group was greater than that of the unexposed group by 0.3 years, and the mean ± SD follow-up period was 7.9 ± 4.6 years. The 3 disease risk modifiers, including BMI category, smoking, and alcohol consumption, were similar between the exposed and unexposed groups; however, data were less likely to be missing in the exposed group compared to the unexposed group.

Table 3. Number, proportion, and causes of death (in order of frequency) in patients without PMR (unexposed group)*

	Unexposed
Total deaths	27,224 (31.0)
Rate per 1,000 patient years (95% CI)	39.2 (38.7–40)
Mortality rate ratio (95% CI)†	1.00 (0.97–1.03)
Causes of death	
Chronic ischemic heart disease	1,810 (6.7)
Chronic obstructive pulmonary disease	1,652 (6.1)
Acute myocardial infarction	1,651 (6.1)
Malignant neoplasm, bronchus or lung	1,631 (6.0)
Bronchopneumonia	989 (3.6)
Atherosclerotic heart disease	967 (3.6)
Pneumonia	889 (3.3)
Alzheimer's disease	790 (2.9)
Malignant neoplasm, breast	709 (2.6)
Vascular dementia	604 (2.2)
Cerebrovascular disease	585 (2.2)
Malignant neoplasm without specification	460 (1.7)
Malignant neoplasm, pancreas	447 (1.6)
Urinary tract infection	416 (1.5)
Malignant neoplasm, colon	410 (1.5)
Malignant neoplasm, esophagus	371 (1.4)
Malignant neoplasm, bladder	312 (1.2)
Congestive heart failure	309 (1.1)
Intracerebral hemorrhage	302 (1.1)
Other respiratory disorders	291 (1.1)
Others	11,629 (41.6)

* Values are the number (%) unless indicated otherwise. 95% CI = 95% confidence interval; PMR = polymyalgia rheumatica.
† This value pertained to the ratio of the mortality rate among the exposed population divided by the mortality rate among the unexposed population.

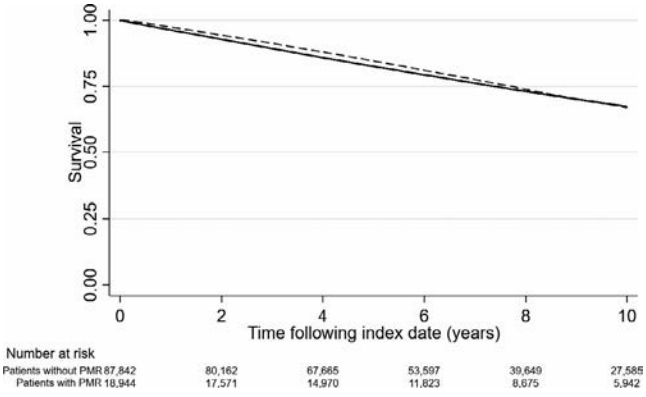

Figure 1. Kaplan-Meier plot of survival in first 10 years following diagnosis date in patients with polymyalgia rheumatica (PMR) (solid line) and without PMR (broken line).

The total number (and proportion) of patients with and without PMR who died, as well as the MMR, and 20 most common causes of death, are shown (Tables 2 and 3). Figure 1 shows the Kaplan-Meier estimate of mortality in the first 10 years after diagnosis in patients with and without PMR. Over the whole time period studied, a slightly higher proportion of patients with PMR died compared to patients without PMR (31.9% and 31.0%). However, the mortality rates were similar, at 39.9 and 39.2 per 1,000 patient-years. Additionally, the MRR of 1.00 (95% CI 0.97–1.03), which was adjusted for age, sex, region, smoking status, BMI category, and alcohol consumption, showed that there was no difference between the 2 groups. A sensitivity analysis, in which patients with coexistent giant cell arteritis were excluded from the sample, revealed the same results.

DISCUSSION

The present study demonstrates that a diagnosis of PMR does not have a significant impact on life expectancy. The causes of death in patients with PMR were broadly similar to those of matched controls; however, a slightly higher proportion of patients with PMR died due to vascular causes, and a slightly lower proportion died due to neoplastic conditions when compared to matched controls.

The present study is the largest study to estimate the effect that a diagnosis of PMR has upon life expectancy. The sample was drawn from a large, established primary care database, which contains patients who are representative of the UK population (11), and is the setting in which PMR is most frequently managed (12). The ONS is the UK's recognized national statistical institute. All deaths in the UK must be registered and are therefore recorded in this data set. This data source is used to report trends in mortality and guide national health care policy; therefore, the ONS data set is the most complete source of this information.

A potential limitation of the present study is the initial ascertainment of PMR. In the CPRD, it is not possible to authenticate diagnoses by ensuring that each patient fulfills validated classification criteria for PMR. No diagnostic criteria nor specific diagnostic test exists for PMR; therefore, even if access to individual patients were possible, confirmation of diagnosis can never be fully achieved. However, ensuring that all patients have at least 2 GC prescriptions in their records provides more confidence in the diagnosis of PMR. This method has been used before in previously published studies in the CPRD of PMR (13). Furthermore, this study can provide reassurance for patients with a diagnosis of PMR that no association with premature mortality was found.

Causes of death may be incorrectly coded. Some studies have estimated, for example, that cardiovascular causes of death may be overstated in mortality data (14). However, a study from the ONS found that only 12% of the broad underlying causes of death needed to be amended following medical examiner scrutiny (15). Furthermore, there is no reason to suppose that the presence of PMR would lead to a difference in error rate compared to those without.

Another potential bias is surveillance bias, wherein people who are diagnosed with PMR may be more likely to be followed up more closely in primary care. This would mean that comorbidities may be diagnosed sooner and treated more effectively in these patients, which could lead to improvement in survival, mitigating any potential reduction in survival caused by the disease itself.

Previous studies have found that patients with PMR have a high comorbidity burden, with a possible increased risk of vascular disease (3,16). In the current study, a greater proportion of patients with PMR had a vascular cause of death recorded. Conversely, a smaller proportion of patients with PMR were recorded as dying due to cancer. Therefore, the neutral effect of PMR on mortality observed in the current study may be caused by the increase in the risk of death due to vascular disease balanced by the reduction in the risk of death due to cancer in patients with PMR.

Two previous studies based in Norway have reported reduced mortality rates in patients with PMR and attributed this reduction to improved medical surveillance of patients with PMR (4,5). One study from the US, however, found no significant difference in mortality in patients with PMR when compared to the general population (6), while another more recent study with >40 years of data also concluded that survival among patients with PMR was no worse compared to the general population (17). In the present study, no significant difference in mortality between patients with PMR compared to matched controls was found, with an adjusted MRR of 1.00 (95% CI 0.97–1.03). These results are therefore reassuring for patients who receive a diagnosis of PMR.

This study is the first to use primary care and linked data to estimate the effect that PMR has on mortality in a large sample of patients. Overall, the mortality rate in patients with PMR, when compared to matched controls, is not significantly different, although there are some minor variations in the recorded cause of death.

However, our previous work (16) demonstrated that patients with PMR were less likely than controls to have a previous diagnosis of cancer or neurological diseases. Therefore, it could be speculated that patients in the PMR group would have been expected to have improved survival when compared to matched controls.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Partington had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Partington, Muller, Mallen, Abdul Sultan, Helliwell.

Acquisition of data. Partington, Abdul Sultan.

Analysis and interpretation of data. Partington, Abdul Sultan, Helliwell.

REFERENCES

1. Partington R, Muller S, Helliwell T, Mallen CD, Abdul Sultan A. Incidence, prevalence and treatment burden of polymyalgia rheumatica in the UK over two decades: a population-based study. Ann Rheum Dis 2018;77:1750–6.
2. Helliwell T, Brouwer E, Pease CT, Hughes R, Hill CL, Neill LM, et al. Development of a provisional core domain set for polymyalgia rheumatica: report from the OMERACT 12 Polymyalgia Rheumatica Working Group. J Rheumatol 2016;43:182–6.
3. Partington R, Helliwell T, Muller S, Abdul Sultan A, Mallen C. Comorbidities in polymyalgia rheumatica: a systematic review. Arthritis Res Ther 2018;20.
4. Gran JT, Myklebust G, Wilsgaard T, Jacobsen BK. Survival in polymyalgia rheumatica and temporal arteritis: a study of 398 cases and matched population controls. Rheumatology (Oxford) 2001;40:1238–42.
5. Myklebust G, Wilsgaard T, Jacobsen BK, Gran JT. Causes of death in polymyalgia rheumatica: a prospective longitudinal study of 315 cases and matched population controls. Scand J Rheumatol 2003;32:38–41.
6. Doran MF, Crowson CS, O'Fallon WM, Hunder GG, Gabriel SE. Trends in the incidence of polymyalgia rheumatica over a 30 year period in Olmsted County, Minnesota, USA. J Rheumatol 2002;29:1694–7.
7. Hippisley-Cox J, Vinogradova Y. Trends in consultation rates in general practice 1995–2009: analysis of the QResearch database. London QResearch Inf Cent Heal Soc Care 2009. URL: https://digital.nhs.uk/data-and-information/publications/statistical/trends-in-consultation-rates-in-general-practice/trends-in-consultation-rates-in-general-practice-1995-2009.
8. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827–36.
9. Dedman D, Ghosh R, Eaton S, Boggon R, Strongman H, Campbell J, et al. ONS death registration data and CPRD primary care data Documentation (Set 16). 2018. URL: https://www.cprd.com/sites/default/files/Documentation_Death_set21_v2.5.pdf.
10. Paskins Z, Whittle R, Sultan AA, Muller S, Blagojevic-Bucknall M, Helliwell T, et al. Risk of fracture among patients with polymyalgia rheumatica and giant cell arteritis: a population-based study. BMC Med 2018;16:1–9.
11. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK primary care data resource. Ther Adv Drug Saf 2012;3:89–99.
12. Yates M, Graham K, Watts R, MacGregor A. The prevalence of giant cell arteritis and polymyalgia rheumatica in a UK primary care population. BMC Musculoskelet Disord 2016;17:285.
13. Smeeth L, Cook C, Hall AJ. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990–2001. Ann Rheum Dis 2006;65:1093–8.
14. Lakkireddy D, Gowda M, Murray C, Basarakodu K, Vacek J. Death certificate completion: how well are physicians trained and are cardiovascular causes overstated? Am J Med 2004;117:492–8.
15. Office for National Statistics. Death certification reform: a case study on the potential impact on mortality. Off Natl Stat 2012;1–17.
16. Partington R, Muller S, Mallen CD, Abdul Sultan A, Helliwell T. Comorbidities in patients with polymyalgia rheumatica prior to and following diagnosis: a case control and cohort study. Semin Arthritis Rheum 2020;50:663–72.
17. Raheel S, Shbeeb I, Crowson CS, Matteson EL. Epidemiology of polymyalgia rheumatica 2000–2014 and examination of incidence and survival trends over 45 years: a population-based study. Arthritis Care Res (Hoboken) 2017;69:1282–5.

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LETTERS

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Trajectories of structural disease progression in knee osteoarthritis: comment on the article by Collins et al

To the Editor:

We read with interest the recently published article by Collins and colleagues (1), which examined trajectories of worsening medial knee compartment joint space width (JSW). Osteoarthritis Initiative (OAI) data from baseline to 8 years of follow-up were used to define 3 JSW trajectories of persons with prevalent symptomatic knee osteoarthritis (OA), based on the presence of baseline pain and Kellgren/Lawrence (K/L) OA grades of 1 to 3. Additionally, the investigators considered an analytic method that allowed for consideration of knee replacement participants, a subgroup whose knee OA data are usually censored in knee OA studies. Finally, the investigators determined trajectories of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores using the 3 trajectories defined from the JSW data as the predictor of WOMAC pain scores over a 9-year period.

We found that the study overall was rigorously conducted and carefully described, but we found that some aspects of the analytic approach and the interpretation of the findings required comment. First, the findings supported 3 latent classes: a stable class, a rapidly progressing class, and a slowly progressing class. In the absence of time of disease onset, as is the case with most OA progression studies, or alternatively, the onset of each K/L grade to account for progression within each K/L grade, the meaning of early versus late structural progression is obscured. For example, the majority of participants in the "early progression" class actually may have had the disease for years prior to OAI enrollment, while most in the "late progression" class may have had a more recent disease onset. For a disease that can take decades to progress, an 8-year snapshot does not seem as informative as one would need, given that the time of disease onset is unknown. For us, an unknown disease onset creates substantial uncertainty about the meaning of the early versus late structural progression trajectories.

Second, the authors opted for smooth trajectory shapes. This choice runs contrary to a V-shaped trajectory type in the presence of an intervention (i.e., before and after knee arthroplasty) that we have documented recently (2). In this case, the time of surgery provides a reference point common across those study participants receiving knee arthroplasty. The knee arthroplasty cases, much like the nonsurgical sample, also appear to lack a meaningful time scale.

Finally, the investigators determined associations between baseline predictors and trajectory class membership. We recently posed a somewhat similar question regarding baseline predictors of good versus poor outcome trajectory membership following knee replacement (2). Contrary to cluster analysis, in latent mixture models, persons belong to all latent classes probabilistically. The probability of a person belonging to all classes sums to unity, by definition. Prior to the analysis, however, the authors converted the posterior probability of belonging to the most likely class to unity and all other conditional probabilities to a null value prior to estimating the regression model. By doing so, Collins et al treated a discrete latent outcome as an observed outcome. This problem has been recognized in the methodology literature, and remedies have been proposed to use a latent discrete variable in the regression model in its original form to avoid biased estimation of regression coefficients (3–5). We also were surprised to see that contralateral knee OA status was not considered as a potential predictor. We found that it was a strong predictor of rapidly progressing knee OA in incident knee OA participants in a prior combined OAI and Multicenter Osteoarthritis study (6).

No potential conflicts of interest relevant to this letter were reported.

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1. Collins JE, Neogi T, Losina E. Trajectories of structural disease progression in knee osteoarthritis. Arthritis Care Res (Hoboken). Arthritis Care Res 2021;73:1354–62.
2. Dumenci L, Perera R, Keefe F, Ang D, Slover J, Jensen M, et al. Model-based pain and function outcome trajectory types for patients undergoing knee arthroplasty: a secondary analysis from a randomized clinical trial. Osteoarthritis Cartilage 2019;27:878–84.
3. Asparouhov T, Muthen BO. Auxiliary variables in mixture modeling: a 3-step approach using Mplus. Struct Equ Modeling 2014;21:329–41.
4. Diallo TM, Lu HZ. On the application of the three-step approach to growth mixture models. Struct Equ Modeling 2017;24:714–32.
5. Cetin-Berber DD, Leite WL. A comparison of one-step and three-step approaches for including covariates in the shared parameter growth mixture model. Struct Equ Modeling 2018;25:588–99.
6. Riddle DL, Stratford PW, Perera RA. The incident tibiofemoral osteoarthritis with rapid progression phenotype: development and validation of a prognostic prediction rule. Osteoarthritis Cartilage 2016;24:2100–7.

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Reply

To the Editor:

We appreciate the letter from Drs. Riddle and Dumenci on our analysis assessing trajectories of JSW progression in knee OA. The authors raise good points about the analytic approach and about interpreting the results in general.

The authors raise a question about the interpretation of early versus late progression in the context of a cohort study enrolling subjects with prevalent knee OA. We describe the so-called "horse-racing effect" in the discussion section of our article and gladly expand here (1). This phrase refers to the scenario where change is already underway at the time a knee OA patient is enrolled in a study, using the analogy in which one would expect to find the faster horses out in front halfway through the race. Here, we mean that knees that have already started progressing are likely to be "out in front" (i.e., have less JSW) at baseline because they were worsening before the start of the study. This is because baseline is simply the point of study enrollment, not the time of disease onset or a "time 0" in disease course. While this may lead to some confusion in the interpretation of early versus late progression (were the "early" progressors subjects who simply had the disease longer?), we still feel that the distinction is meaningful. In practice, for most patients, who may be seeing a health care provider and undergoing radiographs for the first time or considering enrollment in a randomized controlled trial, we will not know the exact moment that they developed OA, but we could use data-driven insights that would help to understand and project the disease progression from that moment forward.

Drs. Riddle and Dumenci ask why we did not consider a V-shaped trajectory, as they undertook such an approach using piecewise latent-class growth analysis to demonstrate a V-shaped trajectory in pain and function following total knee replacement (TKR) in their recent article (2). We were interested in modeling the natural history of OA prior to TKR and therefore treated TKR as an informative dropout. While TKR precludes further assessment of joint structure, piecewise latent-class growth analysis and/or nonsmooth trajectories could certainly be considered to assess changes in pain, function, and other patient-reported outcomes after TKR.

Drs. Riddle and Dumenci offer suggestions regarding assessing the association between covariates and trajectory group membership. We used the standard 3-step approach described in the Guidelines for Reporting on Latent Trajectory Studies, first to determine group number and shape, then to merge trajectory output with original data, and finally to assess the associations between covariates and trajectory groups (3). In scenarios with low entropy, methods that explicitly take into account the uncertainty around trajectory group membership can correct for potential biases due to this uncertainty. Because the main focus of our study was on estimating trajectories, not on finding predictors, we used the standard approach.

Finally, the authors wonder why we did not include contralateral knee OA as a potential predictor for progression, pointing to their own recent work indicating that this condition may be a risk factor for incident knee OA. Risk factors may differ for OA incidence and OA progression, and systematic reviews examining risk factors for OA progression either did not note or found limited evidence for contralateral OA as a risk factor (4,5).

Latent-class growth analysis offers an opportunity to model, describe, and understand heterogeneity in disease course in OA. There are a number of ways to use this methodology and several analytic points to consider, as highlighted by Drs. Riddle and Dumenci in their letter. While different analysts may make alternative modeling decisions, we followed recently published guidelines intended to ensure transparency and reproducibility in these analyses, and we encourage investigators interested in undertaking such analyses to do the same (3,6).

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1. Peto R. The horse-racing effect. Lancet 1981;2:467–8.
2. Riddle DL, Dumenci L. Modeling longitudinal osteoarthritis data to identify homogeneous subgroups: opportunities and challenges in a burgeoning literature. Osteoarthritis Cartilage 2015;23:1035–7.
3. Van De Schoot R, Sijbrandij M, Winter SD, Depaoli S, Vermunt JK. The Grolts-checklist: guidelines for reporting on latent trajectory studies. Struct Equ Modeling 2017;24:451–67.
4. Bastick AN, Belo JN, Runhaar J, Bierma-Zeinstra SM. What are the prognostic factors for radiographic progression of knee osteoarthritis? A meta-analysis. Clin Orthop Relat Res 2015;473:2969–89.
5. Chapple CM, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prognostic studies. Arthritis Care Res (Hoboken) 2011;63:1115–25.
6. Lennon H, Kelly S, Sperrin M, Buchan I, Cross AJ, Leitzmann M, et al. Framework to construct and interpret latent class trajectory modelling. BMJ Open 2018;8:e020683.

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Reviewers

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