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ORIGINAL RESEARCH

Work-related physical strain and development of joint inflammation in the trajectory of emerging inflammatory and rheumatoid arthritis: a prospective cohort study

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ABSTRACT

Objectives Rheumatoid arthritis (RA) mainly affects small joints. Despite the mechanical function of joints, the role of mechanical stress in the development of arthritis is insufficiently understood. We hypothesised that mechanical stress/physical strain is a risk factor for joint inflammation in RA. Therefore, we studied work-related physical strain in subjects with clinically suspected arthralgia (CSA) as a risk factor for the presence of imaging-detected subclinical joint inflammation and the development of clinical arthritis/RA.

Methods In 501 CSA patients and 155 symptom-free persons' occupation-related physical strain was quantified using the International Standard Classification of Occupations. Contrast-enhanced hand-MRIs were made and evaluated for joint inflammation (sum of synovitis/tenosynovitis/osteitis). CSA patients were followed on RA development. Age relationship was studied using an interaction term of physical strain with age.

Results The degree of physical strain in CSA is associated with the severity of joint inflammation, independent of educational-level/BMI/smoking (interaction physical strain-age p=0.007; indicating a stronger association with increasing age). Physical strain is associated with higher tenosynovitis scores, in particular. In symptom-free persons, physical strain was not associated with imaging-detected joint inflammation. Higher degrees of physical strain also associated with higher risks for RA development in an age-dependent manner (HR=1.20 (1.06–1.37)/10-year increase in age), independent of educational-level/BMI/smoking. This association was partly mediated by an effect via subclinical joint inflammation.

Conclusions Work-related physical strain increases the risk of subclinical joint inflammation and of developing RA. The age relationship suggests an effect of long-term stress or that tenosynovium is more sensitive to stress at older age. Together, the data indicate that mechanical stress contributes to the development of arthritis in RA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Considerations of the pathophysiology of rheumatoid arthritis (RA) have so far barely taken into account the mechanical function of the joint and processes related to the onset of arthritis are unidentified. Case–control studies have revealed physical workload as risk factor for RA; but its influence on the pathophysiological trajectory is unknown.

WHAT THIS STUDY ADDS

⇒ The degree of work-related physical strain is associated with the degree of subclinical joint inflammation, and tenosynovitis, in particular, in patients with clinically suspected arthralgia (CSA); this effect is age dependent and present from middle age onwards.

⇒ The degree of work-related physical strain in clinically suspect arthralgia is a risk factor for RA development; this effect is age dependent, has a dose relationship and is mediated by enhancing local joint inflammation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study is the first demonstrating that work-related physical strain in predisposed individuals provides risk for progression to RA, which effect is mediated by more severe subclinical joint inflammation and tenosynovitis, in particular.

⇒ The age relationship in the results point to long-lasting mechanical stress and/or imbalance between microtrauma and recovery of the tenosynovium with increasing age. Further molecular studies at tissue level may decipher the influence of mechanical strain on cells of the immune system in the at-risk phase of CSA.

INTRODUCTION

Rheumatoid arthritis (RA) primarily affects the small joints of the hands and feet and hand joints are also regularly the earliest inflamed.[1] The pathophysiology of RA development is still largely unexplained, but derailment of the autoantibody response is considered one

of the first steps in the onset of RA. Autoantibodies can develop up to 10 years before the occurrence of clinical arthritis and the clinical diagnosis of RA.[2–4] Genetic risk factors (eg, certain HLA-DRB1 alleles) and environmental risk factors (such as smoking and obesity) are considered to promote maturation of the autoimmune response. Increases in anticitrullinated protein antibodies (ACPA)-levels, number of isotypes or autoantibody reactivities occur approximately 5 years before diagnosis.[3–7] Joint symptoms such as arthralgia occur later, generally 6–12 months before diagnosis. During this period, subclinical joint inflammation develops, which may progress to clinically apparent inflammatory arthritis (IA).[8] Processes associated with the development of (subclinical) inflammation in the joint and progression to clinically apparent arthritis during the development of RA are still poorly understood.

Joints are anatomically built to move smoothly. The synovial lining in the joint capsule secretes some synovial fluid for this purpose. Recent anatomical research has shown that the tendons around small hand and foot joints are also surrounded by synovial tissue, the tenosynovium.[9 10] To facilitate flexion and extension of the fingers and toes, this tenosynovium resists shear forces. Therefore, during movement, the joints and surrounding tissues are constantly subjected to mechanical forces. The mechanical role of joints has so far been underexposed in pathophysiological research in RA. Nevertheless, evidence suggests that mechanical stress plays a role in the development of arthritis and RA. Mice studies suggested a role of mechanical forces in disease onset as tensile loading provoked arthritis.[11–13] This effect was independent of the adaptive immune response. Moreover, three case–control studies involving a total of >3800 patients with RA and >6500 healthy controls have revealed excessive repetitive physical load as risk factor for autoantibody-positive and autoantibody-negative RA.[14–16] Similarly, a population-based cohort with >25 000 participants identified manual work as risk factor for RA.[17] The risk effect was independent of socioeconomic status, education, smoking and BMI, suggesting that mechanical stress itself plays a role in the development of RA.

To increase understanding of the multihit process of RA development, we assume that mechanical stress needs further study. Based on the previous work described in mice and humans, and the current knowledge of time sequences during the development of RA, we hypothesised that in people who have developed an autoimmune response and present with joint symptoms, mechanical stress is a risk factor for subclinical joint inflammation and for developing RA. Therefore, we aimed to study the relationship between work-related physical strain and imaging-detected subclinical joint inflammation in arthralgia at-risk for RA (clinically suspected arthralgia (CSA)), and with progression from CSA to clinically apparent IA and RA. The association of work-related physical strain and imaging-detected joint inflammation in symptom-free persons from the general population was studied for comparison.

METHODS

Participants

The relation between work-related physical strain and MRI-detected joint inflammation was studied in 501 consecutive patients presenting with CSA and in 155 symptom-free persons from the general population.

Patients with CSA are considered at-risk for RA due to symptoms similar to RA, while clinical arthritis is (still) absent. Since 2012, consecutively presenting patients with CSA who present at the Leiden rheumatology outpatient clinic have been included in the Leiden CSA cohort. The inclusion criterium for this baseline cohort is small joint arthralgia for <1 year considered suspicious by the treating rheumatologist for progression to RA.[18] Patients were not included if the rheumatologist considered another explanation for the arthralgia (eg, osteoarthritis or fibromyalgia) more likely than imminent RA. Between April 2012 and April 2021, 772 CSA patients were included, of whom 501 patients had undergone an MRI and reported their occupation (full-time students, or unemployed or retired participants were excluded; online supplemental figure SF1). Patients who did or did not report their occupation or did not undergo an MRI scan did not show clinically relevant differences (online supplemental table ST1).

Symptom-free persons were recruited via advertisements in local newspapers and websites. Inclusion criteria were age 18 years or older, no history of RA or other inflammatory rheumatic diseases, no joint symptoms during the previous month and no clinically detectable arthritis on physical examination.[19] 193 symptom-free persons underwent an MRI of whom 155 were employed (online supplemental figure SF2).

Physical strain

Work-related physical strain was quantified using the International Standard Classification of Occupations (ISCO) and self-reported occupation by the participants.[20] The ISCO expresses the physical strain of occupations. During its development, physical strain was measured by the degree of heavy lifting (more than 20 kg (men) or 10 kg (women)) generally present for 307 occupations. This system provides a more gradual quantification than the commonly used distinction between so-called blue and white-collar occupations.[20]

MRI-detected joint inflammation

MRI is a sensitive imaging modality to assess joint inflammation.[21] It is sensitive in detecting synovitis and tenosynovitis and the only imaging modality capable of displaying osteitis.[22 23] At study entry, patients underwent contrast-enhanced 1.5T MRI of a hand (the side with the most symptoms, or the dominant side when symptom severity was symmetrical). Wrist and metacarpophalangeal (MCP(2-5))-joints were evaluated for subclinical joint

inflammation (sum of synovitis, tenosynovitis and osteitis) and were scored according to the RA MRI scoring system and the Haavardsholm method (online supplemental methods SM1).[24 25] Inflammation around interossei tendons in the hands, a recently identified inflammation occurring in CSA and RA, was scored as recently described.[26 27] The symptom-free individuals underwent MRI with the same scanner, scan protocol and scoring methodology as the patients. Previous studies have revealed that some inflammation (especially synovitis, osteitis) can be present in the hands of healthy persons, especially at older age (>60 years).[19 28]

IA development

Patients in the CSA cohort were followed for 2 years for development of IA, defined as joint swelling at physical examination by the rheumatologist. Patients were followed with protocolised visits at 4, 12 and 24 months, and more regular visits in case of increased symptoms, to assess whether IA development had occurred. During follow-up, CSA patients were not treated with DMARDs (including corticosteroids). Among those that developed IA, RA was defined as a clinical diagnosis and fulfilling 1987 and/or 2010 RA criteria at the moment of IA development.[29 30]

Statistics

Association of physical strain and MRI-detected joint inflammation was assessed using multivariable negative binomial regression analysis, determining incidence rate ratios. This analysis was adjusted for age, educational attainment, BMI and smoking as potential confounders, because it is known that MRI-detected joint inflammation increases with increasing age and because previous research showed that socioeconomic status, using educational attainment as a representative factor, was a risk factor for more subclinical joint inflammation in CSA.[31 32] BMI and smoking, although not associated with progression from CSA to RA, were added because these are associated with socioeconomic status.[5 6] Additionally, an interaction between physical strain and age was included to assess the effect of physical strain throughout life. Physical strain and age were centred around the mean to prevent induction of multicollinearity. Physical strain was coded per 10 percentage points and age per 10 years to ease model interpretation. Since MRI-detected subclinical joint inflammation is the sum of synovitis, tenosynovitis and osteitis and physical strain could have different effects on these tissues, the analyses were also done for synovitis, tenosynovitis and osteitis separately.

The association between physical strain according to the ISCO classification and IA development was studied with Cox-regression analysis and also included an interaction between physical strain and age. This analysis was corrected for educational attainment.[31] Although BMI and smoking did not associate with IA development in CSA patients in previous research, and thus may not be considered as true confounders, we also corrected for these factors to increase certainty on observed results.[5 6] Additionally, correction for ACPA status was performed as well as stratification for autoantibody status. As sensitivity analysis, this Cox-regression analysis was repeated with RA development as outcome. Additionally, although the division of blue/white-collar jobs is more crude than the ISCO classification, we performed comparable Cox-regression analysis with blue/white-collar jobs and IA development.

Finally, three-strep mediation analyses according to Baron and Kenny were performed.[33] P values <0.05 were considered statistically significant. IBM SPSS Statistics (V.25) was used.

Patient and public involvement statement

Patient partners were involved in the design of the CSA cohort.

RESULTS

Characteristics of participants

The characteristics of the CSA patients and symptom-free persons are presented in table 1. Mean age of the CSA patients was 43 years, 76% was woman, median tender joint count was 4, 97 (19%) were rheumatoid factor-positive and 63 (13%) patients were ACPA positive (table 1). In symptom-free persons from the general population, the mean age was 47 years, 72% was woman (table 1). Occupations and the concomitant degree of physical strain (according to the ISCO classification) are presented in online supplemental table ST2.

Physical strain and severity of subclinical joint inflammation

Assessment of the association of physical strain and severity of subclinical joint inflammation in CSA revealed that in addition to a (known) association of higher age with more subclinical joint inflammation,[28 32] the interaction between physical strain and age was statistically significant (table 2; IRR=1.05 (1.01–1.08)). This was independent of educational level, smoking and BMI. The interaction indicates that age influenced the relation of physical strain with the degree of subclinical joint inflammation. The IRR is expressed on a multiplicative scale and per 10 percentage points increase in physical strain. The IRR of 1.05 signifies that CSA patients who are 10 years older than average have 1.05-fold increase of their joint inflammation score per 10 percentage points increase in physical strain. For example, CSA patients who are 20 years older have a 1.05*1.05=1.10-fold (10%) increase of joint inflammation score per 10 percentage points increase in physical strain. Additionally, blue-collar jobs on average have about 30% more physical strain than white-collar jobs (table 1, online supplemental table ST2), meaning that 20 years older patients with blue-collar jobs have approximately three fold more joint-inflammation than average aged patients with white-collar jobs. Physical strain (without age-interaction) was not statistically significant (table 2), meaning that the effect of work load was only present at increasing age. To

Table 1 Baseline characteristics of CSA patients and symptom-free persons, also according to occupation type

	All CSA patients N=501	Blue-collar workers* N=189 (38%)	White-collar workers N=312 (62%)	P value
Age, years, mean±SD	43±11	42±12	43±11	0.24
Female, n (%)	383 (76)	145 (77)	238 (76)	1.00
BMI, mean±SD	26.7±5.0	27.5±5.5	26.1±4.5	0.003
Symptom duration in weeks, median (IQR)	21 (9–46)	24 (10–52)	18 (9–40)	0.032
TJC-68, median (IQR)	4 (2–9)	5 (2–10)	4 (2–8)	0.69
ACPA-positive, n (%)	63 (13)	16 (9)	47 (15)	0.037
RF-positive, n (%)	97 (19)	25 (13)	72 (23)	0.007
Increased ESR, n (%)	67 (14)	33 (18)	34 (11)	0.057
Increased CRP, n (%)	101 (20)	48 (26)	53 (17)	0.022
Smoking, n (%)				<0.001
Never	220 (44)	72 (39)	148 (48)	
Former	172 (35)	57 (31)	115 (37)	
Current	103 (21)	57 (31)	46 (15)	
Educational attainment,† n (%)				<0.001
Low	111 (25)	75 (46)	36 (13)	
Intermediate	139 (32)	76 (47)	63 (23)	
High	191 (43)	12 (7)	179 (64)	
Work-related physical strain percentage, median (IQR)	44 (22–63)	58 (50–74)	28 (19–46)	
	All symptom- free persons N=155	Blue-collar workers N=28 (18%)	White-collar workers N=127 (81%)	**P value**
Age, years, mean±SD	47±14	55±13	46±13	0.001
Female, n (%)	110 (71)	16 (57)	94 (74)	0.11
BMI, mean±SD	24.7±3.9	25.9±4.3	24.4±3.8	0.056
Smoking, n (%)				0.15
Never	83 (54)	11 (39)	72 (57)	
Former	58 (37)	15 (54)	43 (34)	
Current	14 (9)	2 (7)	12 (9)	

*Service workers, shop and market sales workers, skilled agricultural and fishery workers, craft and related trades workers, plant and machine operators, assemblers and workers in elementary occupations.
†Low: primary school or pre-vocational secondary education. Intermediate: higher secondary education, preparatory scientific education, vocational college. High: university or university of applied sciences.
ACPA, anticitrullinated protein antibodies; BMI, body mass index; CRP, C reactive protein; CSA, clinically suspect arthralgia; RF, rheumatoid factor; TJC, tender joint count.

make the age-effect more insightful, figure 1A depict the associations between physical strain and subclinical joint inflammation at different age categories. This depiction suggested that the effect was present in patients with CSA who were approximately 50 years of age or older.

The association of physical strain and subclinical joint inflammation was also independent of the presence of ACPA (online supplemental table ST3) and was also present when autoantibody-positive and negative patients were studied separately (online supplemental table ST4).

Since subclinical joint inflammation is the sum of synovitis, tenosynovitis and osteitis and physical strain could have different effects on these tissues, the analyses were done for synovitis, tenosynovitis and osteitis separately. In addition to the known association of age with all of these inflamed tissues, this revealed a significant interaction of physical strain and age for tenosynovitis (IRR 1.09 (1.05–1.14) per 10 years increase in age, online supplemental table ST5), and not for synovitis and osteitis. This suggests that an effect of work-related physical strain at higher age on the joint was mostly driven by an effect on the tenosynovium. Figure 1B depicts the association of physical strain and tenosynovitis in CSA for different age categories. Physical strain also showed a tendency towards more interosseous tendon inflammation in the hands (IRR 1.11 (0.98–1.26) per 10-year increase in age; online supplemental table ST6).

Table 2 Work-related physical strain at increasing age associated with the severity of MRI-detected joint inflammation in CSA patients but not in symptom-free controls

	CSA patients IRR (95% CI)	Symptom-free controls IRR (95% CI)
Interaction Physical Strain × Age	**1.05 (1.01 to 1.08)**	0.98 (0.93 to 1.04)
Physical strain (per 10 percentage-points increase)	1.01 (0.98 to 1.05)	1.06 (0.98 to 1.14)
Age (per 10 years increase)	**1.41 (1.29 to 1.53)**	**1.83 (1.56 to 2.15)**
BMI (per point increase)	1.00 (0.98 to 1.02)	1.03 (0.98 to 1.08)
Smoking		
Never	(ref)	(ref)
Former	0.93 (0.74 to 1.18)	1.05 (0.70 to 1.58)
Current	1.05 (0.80 to 1.34)	1.28 (0.61 to 2.66)
Low educational attainment	1.06 (0.83 to 1.35)	–
Intercept	5.94 (5.08 to 6.94)	3.40 (2.62 to 4.41)

Statistically significant associations are displayed in **bold**. Analyses are performed in CSA patients and symptom-free controls of all age-groups. The IRR is interpreted on a multiplicative scale. The IRR for the interaction term physical Strain×Age is statistically significantly>1.0, indicating that physical strain is positively associated with subclinical inflammation at higher ages. The IRR for the interaction term describes – for every 10 years increase in age of the CSA patient—the *additional* relative increase in subclinical inflammation score per 10 percentage points increase in physical strain. In other words, the IRR of 1.05 signifies that CSA patients who are 10 years older than average, have an additional 1.05 fold increase of their total MRI-detected subclinical inflammation score per 10 percentage points increase in physical strain. Likewise, CSA patients who are 20 years older than average have an additional 1.05*1.05=1.10 fold (10%) increase of their MRI-detected subclinical inflammation score per 10 percentage points increase in physical strain. To make the interpretation of this interaction more insightful, the relation between physical strain and MRI-detected inflammation at different ages is presented in figure 1. Educational attainment data were not available in the symptom-free persons.
BMI, body mass index; CSA, clinically suspect arthralgia; IRR, incidence rate ratio.

Physical strain and MRI-detected joint inflammation in the general population

Because subtle MRI-detected joint inflammation is present in the general population and especially at higher age,[19] we studied whether physical strain also influenced the extent of MRI-detected joint inflammation in the normal situation, which would imply a general and not disease-specific effect. This revealed that physical strain was not statistically significantly associated with MRI-detected joint-inflammation (table 2).

Physical strain and development of IA and RA

The association of the degree of physical strain with progression to IA during a mean follow-up of 25 months was studied in the total CSA population. In total, 63 (12%) of the CSA patients developed IA, of whom 28 (44%) were ACPA positive and 36 (57%) were ACPA negative. Physical strain at increased age (the interaction of physical strain with age) was significantly associated with IA development: HR=1.28 (1.15–1.42). Also here, physical strain was not a risk factor without considering age (table 3). The association of the degree of physical strain at increased age and IA development was independent of educational level, BMI and smoking (table 3), and also independent of ACPA status (HR=1.18 (1.08–1.30); online supplemental table ST7).

RA classification criteria were met in 43/63 (68%) of the patients who developed IA; 28 of these patients were ACPA positive and 15 ACPA negative. The association of work-related physical strain was also present when studying RA development as outcome (HR=1.20 (1.06–1.37)/10-year increase in age; online supplemental table ST8).

Figure 2A depicts the risk of work-related physical strain categorised into tertiles for progression to IA, showing a dose relationship with the highest rate of progression in patients with the highest level of physical strain in CSA patients aged ≥50 years. There was no increased risk for IA observed in CSA patients aged <50 years (online supplemental figure SF3).

When assessing blue-collar and white-collar occupation (a more crude categorisation than the ISCO quantification), patients with blue-collar occupations also had an increased risk for developing IA, although with a broader CI (HR=1.37 (0.86–2.16) for the interaction blue-collar/white-collar occupation×age in the total population; visually depicted in figure 2B for patients aged ≥50).

Physical strain and educational attainment

Lower educational attainment in CSA is a known risk factor for progression to IA that is not explained by BMI and smoking.[5 6 31] We evaluated the relation between educational attainment and blue/white-collar jobs; this revealed only a partial overlap (online supplemental figure SF4). In addition, we performed a mediation analysis to investigate whether the risk of educational attainment was explained by work-related physical strain. This showed that educational attainment was associated with

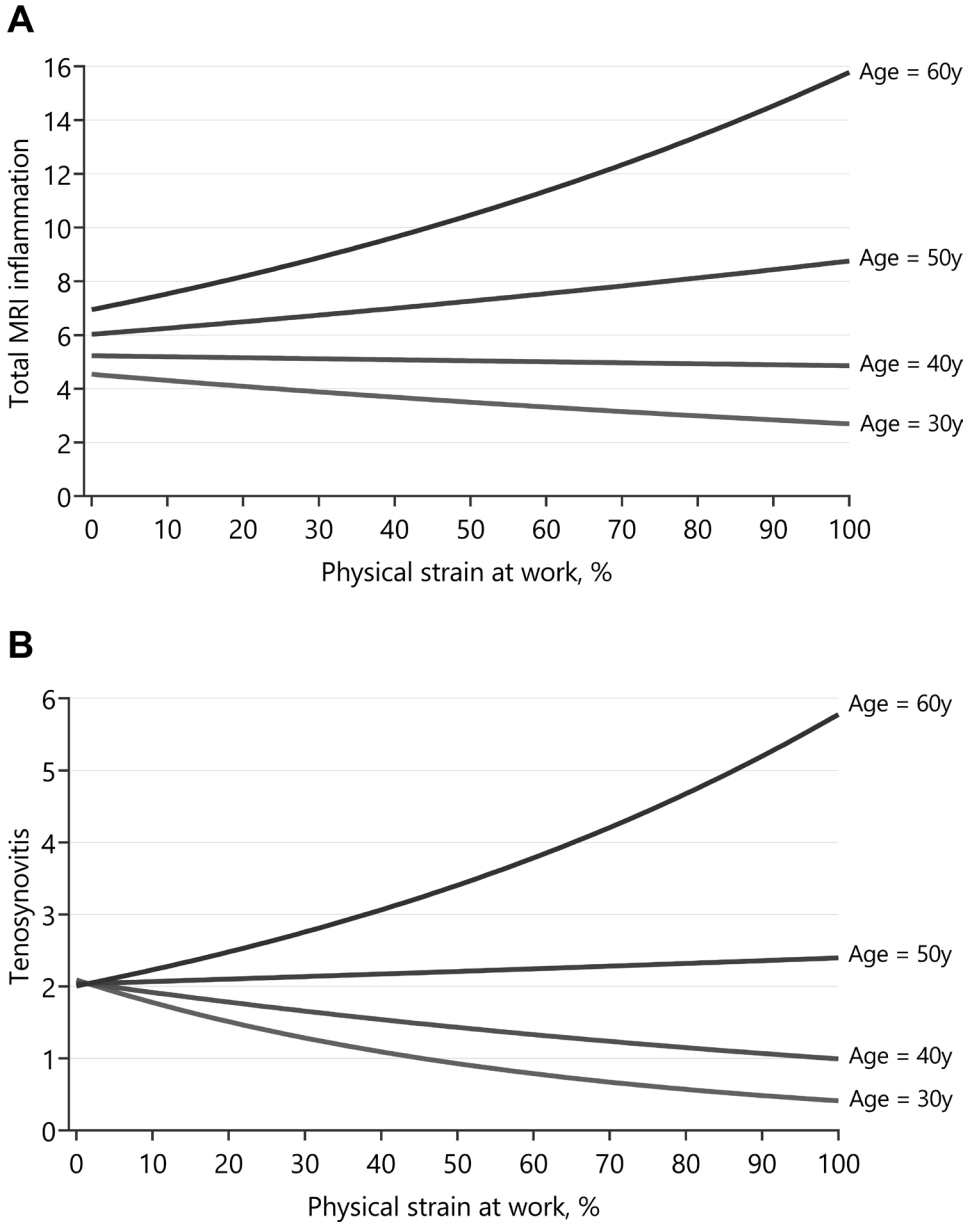

Figure 1 Visual presentation of association between physical strain and MRI-detected subclinical joint inflammation (A) and tenosynovitis (B) at different ages—in CSA. Curves depict the total MRI inflammation score (A) or tenosynovitis score (B) predicted by the multivariable negative binomial regression model from table 2 assuming 'average patients' with average BMI (26.7 kg/m^2), who are never-smokers who have intermediate or high educational attainment for different ages. BMI, body mass index; CSA, clinically suspect arthralgia; y, years.

the degree of physical strain and physical strain with IA development (figure 3A). Moreover, the statistical significance of the association between educational attainment and IA development did not remain statistically significant after adjusting for physical strain (figure 3A). This suggests that the recently observed risk of educational attainment was partly mediated by the effect of work-related physical strain.

Association of physical strain with arthritis development mediated by subclinical joint inflammation

Finally, we determined whether the increased risk of physical strain in CSA for developing IA is related to its effect on subclinical joint inflammation. This was also studied with mediation analyses (figure 3B). The degree of subclinical joint inflammation was associated with IA development. The association of physical strain and IA development lost statistical significance when adjusting for the degree of physical strain. This implies that subclinical joint inflammation is a mediator in the path of physical strain to IA development.

DISCUSSION

The mechanical function of hand joints has so far been barely considered in the pathophysiology of RA and risk factor studies. We set out to study the role of mechanical stress in the development of RA, postulating that

Table 3 Association of the degree of physical strain at work with development of clinically apparent inflammatory arthritis

	Multivariable HR (95% CI)
Interaction* Physical Strain × Age	1.28 (1.15 to 1.42)
Physical strain (per 10 percentage-points increase)	0.93 (0.83 to 1.04)
Age (per 10 years increase)	1.10 (0.85 to 1.43)
Low educational attainment	1.77 (0.98 to 3.17)
BMI (per point increase)	0.94 (0.88 to 0.999)
Smoking	
Never	(ref)
Former	1.11 (0.58 to 2.13)
Current	2.09 (1.08 to 4.07)

Analyses are performed in CSA patients of all age-groups.
*The HR for the interaction term describes—for every 10 years increase in age of the CSA patient—the *additional* relative increase in hazard for clinical arthritis development per 10 percentage points increase in physical strain. In other words, the HR of 1.28 signifies that CSA patients who are 10 years older than average, have an additional 1.28-fold (28%) increase of their hazard for clinical arthritis development per 10 percentage points increase in physical strain. Likewise, CSA patients who are 20 years older than average have an additional 1.28*1.28=1.64 fold (64%) increase of their hazard per 10 percentage points increase in physical strain.
BMI, body mass index; CSA, clinically suspect arthralgia.

mechanical strain, a consequence of the joint mechanical function, is involved in developing subclinical joint inflammation and progression to clinical arthritis and RA. Several large case–control studies had revealed that repetitive mechanical loading is associated with RA.[14–17] Our longitudinal study demonstrated that the severity of work-related strain is associated with subclinical joint inflammation in the risk stage of CSA. We also identified a dose relationship between work-related physical strain with risk for further progression to clinical arthritis and RA. These data identify mechanical stress as risk factor.

The effect of physical strain on MRI-detected joint inflammation in CSA and on RA development was independent of smoking and high BMI. This is in line with results from case–control studies that showed that the association of physical workload with RA was independent of factors that are related to socioeconomic status such as smoking and obesity.[14–17] Physical strain seems, therefore, not related to known environmental risk factors for RA (smoking, obesity) but an independent and relatively new risk factor for RA. Moreover, it has been recently described that lower educational attainment is a risk factor for RA development in CSA.[31] This risk was independent of BMI and smoking and remained 'unexplained'.[31] Our data revealed that work-related physical stain partly explains the association of educational attainment with RA risk.

Interestingly, our data suggest that local mechanical stress may play a role in 'homing' autoimmune responses to the joint. While some MRI-detected 'inflammation' is known to prevail in the general population, especially at increasing age, mechanical strain was not associated with the severity of this MRI-detected inflammation in symptom-free persons in the healthy setting. Although the group size of the healthy group was smaller than that of the CSA population and larger studies in healthy individuals may be of interest, a current type II error is less likely because the data showed no tendency for an effect. In persons who are in the risk-stage of CSA, mechanical strain was associated with subclinical joint inflammation and an increased risk for progression to RA. Mediation analyses suggested that physical strain exerted its effect on RA-development via aggravating subclinical joint inflammation as intermediate step. The absence of the association in the healthy setting suggests a disease-related effect rather than a general phenomenon. People with CSA are known to have a systemic autoimmune/auto-inflammatory response that is abnormal for months up to years.[4 7 34] Presumably these processes have made the joint vulnerable to the influence of mechanical stress. This study sheds light on time sequences by suggesting that, after earlier abnormalities in systemic autoimmune responses, mechanical factors are a subsequent pathophysiological hit to the development of RA.

The association of physical strain with subclinical joint inflammation was age dependent; while physical strain in younger age groups was not associated with more subclinical joint inflammation, the graphical depiction suggested that a positive association was present from about age 50. Also the risk for RA was identified in the total CSA population, stratification for age showed that physical strain was a risk factor especially in patients aged ≥50, but not in patients aged <50 years. The finding of confinement to middle age and older at-risk persons can be explained as that only prolonged physical strain is a risk factor. Since information on the duration per occupation was not collected, the presumption that long-lasting physical strain is underlying the statistical association of physical work strain with age could not be verified. However, this would fit the observation done in a large case–control study that prolonged repetitive physical workload is a risk factor for RA.[15] This study even showed a dose relationship between frequency (days per week) of repetitive physical workload during 5 years and the odds of RA.[15] An alternative explanation for the relationship of physical strain with age would be that joint tissues become more vulnerable to mechanical stress in middle and older age, for example, because repair mechanisms are less able to compensate for common microtraumas. Further studies are needed to determine whether either mechanical strain that is prolonged for many years/decades or repetitive mechanical strain at older age is underlying the age dependency of the effect, or whether

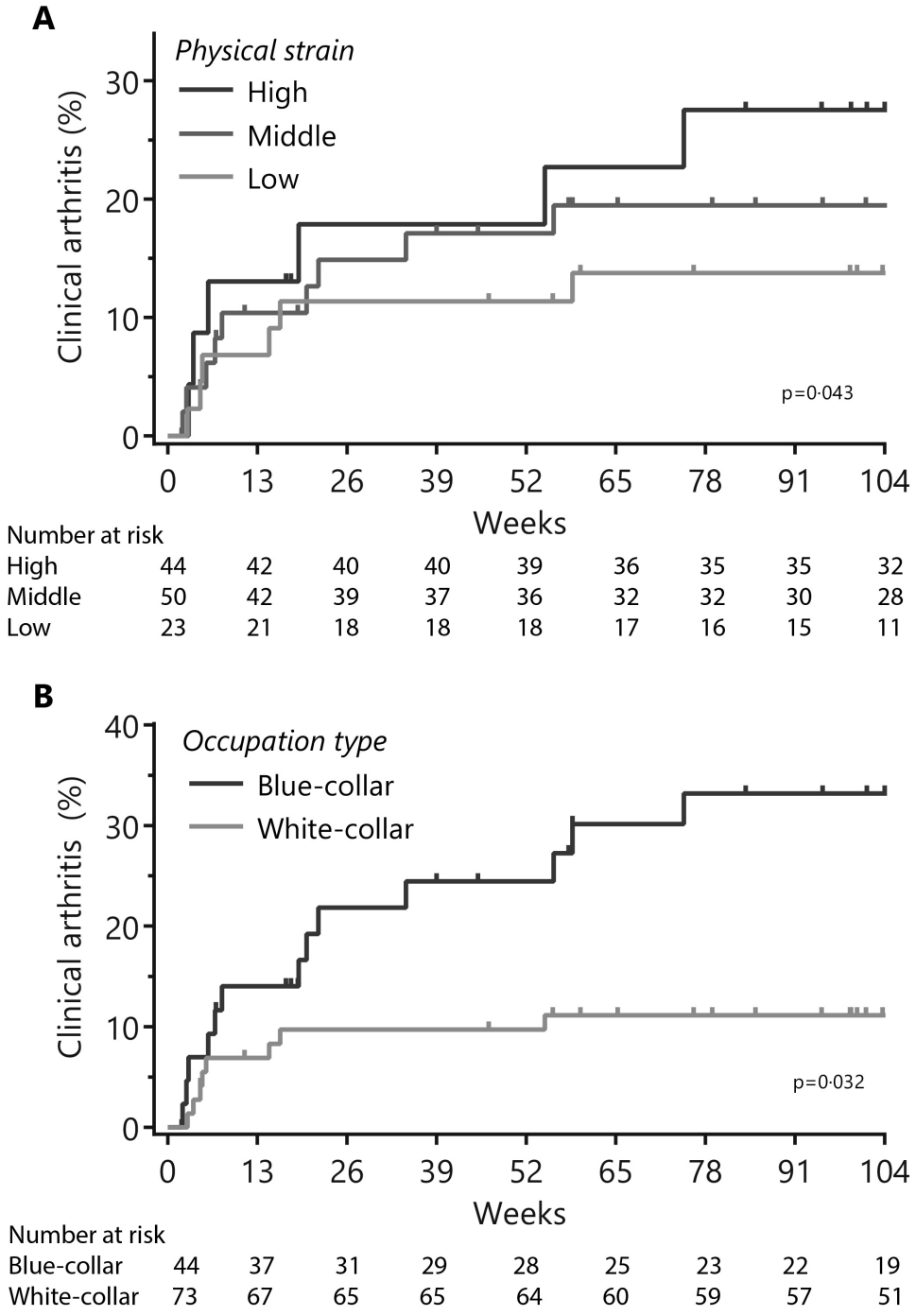

Figure 2 Progression to clinically apparent inflammatory arthritis according to (A) severity of work-related physical strain and (B) occupation type in CSA patients aged ≥50 years. Associations between physical strain (A: tertiles of degree of work-related physical strain according to ISCO; B: occupation type (blue-collar vs white-collar)) and IA development are shown. Because an age-dependent effect of physical strain captured as an interaction between physical strain and age cannot be shown in a Kaplan-Meier curve, these figures present associations in CSA patients aged ≥50 years. The Kaplan-Meier curves of CSA patients <50 years did not show differences between the tertiles of physical strain. CSA, clinically suspect arthralgia; ISCO, International Standard Classification of Occupations.

both explanations may be valid. Moreover, and intriguingly, it could be speculated that the relationship with age shown here could even contribute (together with other contributing factors, for example, hormonal factors or systemic immunological changes called 'immunosenescence') to the fact that RA mainly occurs in the second half of life. This would mean that a number of risk-promoting processes accumulate in the second part of life, ultimately promoting the development of arthritis and RA.

An imbalance between (long-lasting) physical strain and local repair may help explain how subclinical joint inflammation develops and/or progresses to clinical arthritis and RA. Our study demonstrated that physical

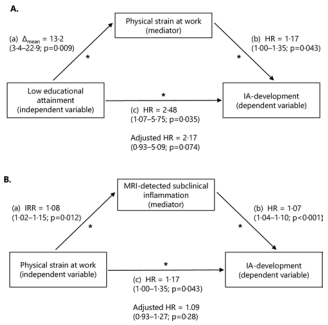

Figure 3 Mediation analyses showing that work-related physical strain partly mediated the relation between educational attainment and IA development (A) and that subclinical joint inflammation partly mediated the relation of physical strain at work with IA development (B) 95% CIs are shown between brackets. Statistically significant associations are marked by an asterisk (*). Mediation analyses were performed in CSA patients aged 50 years and older and in line with Baron and Kenny in order to elucidate on the causal path of physical strain (according to the ISCO classification) to IA development.[20 37] CSA, clinically suspect arthralgia; IA, inflammatory arthritis; IRR, incidence rate ratio; Δ_{mean}, mean difference in physical strain at work of low vs intermediate/high educational attainment.

strain was related to tenosynovitis in particular. Recent anatomic studies have revealed that tenosynovium is present around tendons of small joints of the hands and forefeet.[9 10] These sheaths of synovial tissue are subjected to shear stress, in particular. Prolonged mechanical stress can provoke local microtrauma. A study in mice with induced arthritis showed tenosynovitis as the first local phenomenon that preceded intra-articular inflammation.[35] Moreover, tenosynovitis in CSA has been observed to predict progression from CSA to RA and has been suggested as relevant hallmark of RA.[8 36] The combination of these previous and current findings increase the interest in the tenosynovium as pivotal tissue of RA development. We propose a role for mechanically induced microtrauma in the tenosynovium-sparking chronic joint inflammation during RA development. Further studies are needed for molecular characterisation of the tenosynovium in health and RA and to investigate the influence of mechanical stress on this molecular composition.

The risk provided by work-related mechanical strain was statistically independent of ACPA. Mice studies showing that tensile loading provoked arthritis revealed that this effect was independent of the adaptive immune response.[11 12] Repetitive mechanical strain induced local complement activation, increased danger-associated molecular pattern expression, activating Fcγ receptors as well as changes in fibroblast phenotypes.[12] Although the most commonly known genetic and environmental risk factors are limited to autoantibody-positive RA, mechanical stress may indicate a 'common factor/pathway' in autoantibody-positive and autoantibody-negative disease by which subclinical joint inflammation develops or progresses to clinical arthritis and RA.

This study has limitations. We studied work-related physical strain and did not collect information on mechanical loading due to activities in leisure time. However, a case–control study identified work-related physical activity as factor with increased risk for RA, in contrast to physical activity in leisure time.[14] This may point to a difference in (cumulative) dose of physical strain. Another limitation is that we did not collect detailed information on the type of physical loading. Previously it has been observed that repetitive hand/finger movements, repetitive bending, lifting more than 10 kg and hand above shoulder level work all were risk factors.[15] Future epidemiological studies with detailed questionnaires can shed light on the risk provided by different types of physical loading on joint inflammation and RA development in CSA. Additionally, immunological studies are required to determine the influence of mechanical strain on cells of the immune system and joint tissue in the at-risk phase of CSA.

The current data about long-term physical strain do not imply to discourage physical exercise. Based on current data, we would also not suggest that patients at-risk for RA should discontinue working or should avoid long-term physical strain. Whether such interventions would aid in preventing the development of RA should first be studied in clinical trials. Prolonged physical strain (in certain jobs) may be (even) more difficult to avoid or address, than environmental factors like smoking or obesity. The value of the current findings is increased understanding of environmental risk factors in the trajectory of the development of RA. Recognising that mechanical factors can contribute to the development of arthritis, in addition to known changes in the adaptive immunity, is an important new angle that can promote further research to increase the understanding of RA development.

Suggested is follow-up research on tissue of predisposed patients who do or do not progress to RA. This may reveal mechanisms that contribute to disturbed homeostasis and the development of chronic inflammation. Such results may provide opportunities for targeted intervention in the future.

In conclusion, considerations of the pathophysiology of RA have so far barely taken into account the mechanical function of the joint. This study is the first demonstrating that work-related physical strain in CSA provides risk for progression to RA, which effect is mediated more severe subclinical joint inflammation and tenosynovitis, in particular. The age relationship in the results point to long-lasting mechanical stress as a critical factor in arthritis development in RA.

Contributors BTvD and AHMvdHvM were involved in study concept and design. BTvD, SJHK, NKdH contributed to the collection of data. BTvD and SJHK performed the data analysis. BTvD and AHMvdHvM interpreted the results. BTvD, AHMvdHvM, SJHK and AMPB wrote the manuscript. All authors critically revised the manuscript and approved the final version. BTvD and AHMvdHvM are the guarantors for this manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Research protocols for the Leiden CSA-cohort and for MRI in symptom-free individuals (P11.210) was approved by the local Medical Ethical Committee of the Leiden University Medical Center (LUMC) and all participants provided written informed consent. Participants gave informed consent to participate in the study before taking part.

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