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ORIGINAL ARTICLE

Physical workload is associated with increased risk of rheumatoid arthritis: results from a Swedish population-based case–control study

Pingling Zeng,[1,2] Lars Klareskog,[2] Lars Alfredsson,[1,3] Camilla Bengtsson[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Pingling Zeng;
pingling.zeng@ki.se

ABSTRACT

Objectives: This study investigated: (1) the association of physical workload (PW) and risk of rheumatoid arthritis (RA); (2) the potential interactions between PW and the genes in the human leucocyte antigen (HLA) region.

Methods: A population-based case–control study involving incident cases of RA (3150 cases and 5130 controls) was performed using data from the Swedish Epidemiological Investigation of Rheumatoid Arthritis. Information on 7 types of self-reported PW exposure and *HLA-DRB1* genotypes of cases and controls were gathered. Anticitrullinated protein antibody (ACPA) status of cases was identified. For each PW exposures, exposed participants were compared with unexposed participants. ORs with 95% CIs of RA (overall), ACPA-positive RA and ACPA-negative RA associated with different PWs were estimated using logistic regression. HLA-PW interactions were estimated using the principle of departure from additivity of effects by calculating attributable proportion (AP) due to interaction.

Results: ORs of developing RA associated with 6 various PW exposures ranging from 1.3 (95% CI 1.1 to 1.4) to 1.8 (95% CI 1.6 to 2.0) were observed. Exposure to more types of PW was associated with increasing risk for RA (p<0.0001). No major difference in the ORs between ACPA-positive and ACPA-negative RA was found. For some exposures, we found evidence of interactions between PW and the *HLA-DRB1* shared epitope genes, regarding risk of ACPA-positive RA (AP: from 0.3 (95% CI 0.1 to 0.5) to 0.4 (95% CI 0.2 to 0.6)).

Conclusions: PW is associated with the risk of ACPA-positive and ACPA-negative RA. Interactions between PW and the *HLA-DRB1* shared epitope were found in ACPA-positive RA.

Key messages

What is already known about this subject?

- Prolonged repetitive physical workload has been shown as a risk factor for osteoarthritis but has not been systematically studied as a risk factor for inflammatory rheumatoid arthritis (RA).

What does this study add?

- Prolonged repetitive physical workload is associated with an increased risk of anticitrullinated protein antibody (ACPA)-positive and ACPA-negative RA.
- The gene–environment interaction between certain types of prolonged repetitive physical workload and the *HLA-DRB1* shared epitope may be involved in ACPA-positive RA aetiology.

How might this impact on clinical practice?

- These findings highlight the importance of considering prolonged repetitive workload when studying risk factors for inflammatory arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by inflamed synovial tissues which can result into joint destruction and progressive disability. The development of RA is a consequence of genetic predisposition and environmental triggers. The most widely replicated environmental risk factor for RA is cigarette smoking.[1–4] Other environmental factors associated with RA risk include particle exposure such as silica and textile dust.[5–8] In contrast, moderate alcohol consumption appears to have a protective effect.[9] It is likely that additional environmental and lifestyle factors that enhance or protect against RA exist. Identification of such factors may contribute to RA prevention and lead to a better understanding of the disease pathogenesis. Physical workload (PW) has been identified as a risk factor for non-autoimmune osteoarthritis and low back pain,[10–13] and it is an obvious exposure to consider for all types of joint problem. To

the best of our knowledge, PW has however not been systematically studied as a risk factor for RA.

Some identified important environmental factors (particularly smoking) have been shown to interact with the major histocompatibility complex class II alleles, initially defined by the classic *HLA-DRB1* shared epitope (SE), which is a genetic risk factor for anticitrullinated protein antibodies (ACPA)-positive RA.[14–17] It has recently been shown that the interaction between smoking and human leucocyte antigen (HLA) polymorphisms relies on specific amino acid sequences in the peptide-binding groove of the HLA-DR molecule.[18] Furthermore, such gene–environment interactions seem to vary across subtypes of RA defined by the presence or absence of ACPA targeting different citrullinated peptides.[19–22] Against this background, studies on potential novel environmental factors should include analyses of possible gene–environment interaction between environmental exposures and relevant genes, in particular the *HLA-DRB1* variants.

In this study, we asked the following questions: (1) Is PW associated with the development of RA (overall), ACPA-positive RA and ACPA-negative RA? (2) If PW is a risk factor for RA, is there a gene–environment interaction between PW and *HLA-DRB1* SE-related genes regarding ACPA-positive RA?

PATIENTS AND METHODS

Study design

This study used data from the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA), a population-based case–control study involving incident cases of RA. The study base was defined by the population aged 18–70 years of age in parts of Sweden from 1996 to 2014. A detailed description of the EIRA study design has previously been published.[4]

Identification of cases and controls

Cases were defined as those who were newly diagnosed with RA based on the American College of Rheumatology (ACR) 1987 or 2010 criteria for the classification of RA. Cases were recruited from all hospital-based rheumatology units and almost all private rheumatology clinics in the study area and were examined by rheumatologists at these units.

Controls were randomly chosen from the national population and were matched with potential cases by age, sex and residential area. One control was selected per case (close to the time of including the case) during the recruitment period 1996–2006; two controls were selected per case during the recruitment period 2006–2014. If a control declined to participate then another control was selected using the same principles. If a control was matched to a case, but the case was later excluded from the study due to not fulfilling the ACR criteria, the control was nevertheless retained in the non-matched analyses.

Data collection

All cases and controls were invited to answer a questionnaire. Incomplete answers were completed through mail or telephone by trained staff. The cases received their questionnaire at the time when they were first diagnosed with RA. The mean time between the experience of first disease symptom to diagnosis was 10 months, and for 85% of the cases, the time length was less than a year. A blood sample was collected from patients during their first visit to the rheumatology clinic. Blood samples from controls were collected at local medical units and sent to our laboratory by postal service.

In total, 3973 RA cases and 7681 controls were invited to the study, of which, 3724 (94%) cases and 5935 (77%) controls completed the questionnaire. Blood samples were received from 3680 (99%) of the cases and 3281 (55%) of the controls who completed the questionnaire (only controls that answered the questionnaire were asked to provide a blood sample). A separate methodological study has demonstrated that the group of cases and controls that provided blood samples represents well the entire group of cases and controls, respectively, that answered the questionnaires regarding demographic characteristics, environmental exposures and lifestyle factors.[23] A total of 44 cases were excluded from this study due to missing information on ACPA status.

Consent of participation was received from all patients and controls. The study was approved by the ethics committee of the Karolinska Institute.

Assessment of exposure to PW

Information on PW was collected from eight questions about work-related physical stress at baseline and 5 years before baseline. Baseline was defined as the year when the participants answered the questionnaire (ie, at the time of diagnosis for the patients). The questions asked about work postures and movements are shown in table 1. A more detailed description of the questions is shown in the online supplementary appendix. We defined seven different work postures and movements mentioned in the questionnaire as seven different types of PW. The questions resemble the Dutch Musculoskeletal Questionnaire which measures self-reported musculoskeletal workload with acceptable validity.[24 25] Our questions, with six possible response categories, asked about the frequency and length of time spent in different activities. In the questions, emphasis was given on time length (eg, more than a total of 30 min per day) and often repeated (eg, several times per hour or per minute) efforts. Participants who answered 'none', 'never or rarely' or 'not at all' were considered as unexposed to the type of PW referred to in the question. Participants who chose all other answers (except 'not working') were considered as exposed to the type of PW referred to in the question. Participants who answered 'not working' at baseline were excluded from the baseline analyses; participants who answered

Table 1 Questions regarding work-related prolonged repetitive physical workload in the EIRA questionnaire

Types of physical workload	Questions
Repetitive bending/turning	Does/did your work require you to bend over or turn in a repetitive manner several times per hour?
Repetitive hand/finger movements	Does/did your work involve performing repetitive hand or finger movements several times per minute? (eg, typing or sorting)
Carry or lift more than 10 kg	Do/did you lift or carry objects heavier than 10 kg?
Precision work	Does/did your work require you to perform precision work for more than a total of 2 hours per day? (eg, fine mechanics, clock-making or dental work)
Hands below knee level	Does/did your work involve movements where your hands are/were placed below knee level for more than a total of 30 min per day? (eg, floor or ground work)
Hands above shoulder level	Do/did you perform work where your hands are/were placed above shoulder level for more than a total of 30 min per day?
Vibration	What proportion of your working day do/did you work on a vibrating floor or seat? (eg, in a car, boat, aeroplane, tractor or lorry)
Vibration	What proportion of your working day do/did you work using vibrating hand-held machines? (eg, power drill, sander, nail gun, chainsaw, levers, steering wheels, etc)

EIRA, Epidemiological Investigation of Rheumatoid Arthritis.

'not working' 5 years before baseline were excluded from the 5 years before baseline analyses (table 2). Individuals (530 (14%) cases and 805 (14%) controls) who reported not working both at baseline and 5 years before baseline were excluded from this study. The most frequent occupations of those who were exposed to all seven types of PW 5 years prior to baseline were: metal machine work/building metal work (14%), electrical and electronic work (13%), and building and construction work (12%; see online supplementary table S1).

Antibody assays and genotyping

ACPA was measured from the blood samples using enzyme-linked immunosorbent anti-CCP2 assay (Immunoscan RA Mark2, Euro-Diagnostica, Malmo, Sweden). The positivity cut-off value was 25 units/mL.[26 27]

HLA-DRB1 genotypes were analysed using sequence-specific primer-PCR (DR low-resolution kit; Olerup SSP, Saltsjöbaden, Sweden). The procedures have been previously described.[14] Among *HLA-DRB1* genes *DRB1*01*, *DRB1*04* and *DRB1*10* genes were defined as 'SE'.

Potential confounding factors

Age, residential area, sex, body mass index (BMI <25 or ≥25 kg/m^2), cigarette smoking (<10, 10–19 and ≥20 pack-years; 1 pack-year is equivalent to smoking 20 cigarettes per day for 1 year), educational level (university degree, yes or no), recruitment time period (1996–2006 and 2006–2014), alcohol consumption (non-drinkers, low, moderate, high), silica exposure (rock drilling, stone crushing or stone dust, yes or no) and occupational classes (manual workers and non-manual employees; based on the socioeconomic classification system of Statistics Sweden) were considered as potential confounding factors. In addition, all types of PW exposure in this study were considered as potential confounding factors for each other.

Statistical analysis

ORs with 95% CIs were calculated for the development of RA (overall RA or ACPA-positive RA or ACPA-negative RA) associated with PW using unconditional logistic regression. Conditional logistic regression analyses (matched analyses) were also performed and the results resemble closely those from the unconditional analyses. Owing to the availability of larger number of controls, especially when analysing RA subsets, the results from the unconditional logistic analyses were presented in this study as these entail higher statistical power and exhibit narrower CIs. All analyses were adjusted for the matching variables (age, sex and residential area). No substantial alteration of OR values was observed after adjusting for all the potential confounding factors aforementioned; thus, these were not retained in the final analyses.

A test for trend was performed between number of PW exposures and the OR of developing RA. The PW exposures were categorised into seven groups, with groups 0–6 corresponding to exposure to none of the six types of PW exposure (repetitive bending/turning, repetitive hand/finger movements, lift or carry more than 10 kg, hands below knee level, hands above shoulder level and vibration) and exposure to all of the six types PW exposure, respectively. Exposure to precision work was excluded in this analysis, because it was not significantly associated with the outcome.

The interaction between PW and SE was evaluated on the additive scale, using the principle of departure from additivity of effects.[28] ORs were calculated using unconditional logistic regression by comparing the double exposed group (participants exposed to SE and PW) and single exposed group (participants exposed to only SE or only PW) with the unexposed reference group (participants unexposed to SE and PW). The attributable proportion (AP) due to interaction with 95% CI was then calculated based on the obtained ORs values.[29]

Table 2 Characteristics of participating cases and controls in the EIRA

	RA cases			
	RA overall (n=3150)	ACPA-positive (n=2094) (66%)	ACPA-negative (n=1056) (34%)	Controls (n=5130)
Age, mean±SD	51±12	51±12	52±12	52±13
Female (%)	2252 (71)	1514 (72)	738 (70)	3655 (71)
BMI≥25 (%)	1482 (47)	944 (45)	538 (51)	2324 (45)
Smoking status (%)				
Never	1023 (32)	624 (30)	399 (38)	2301 (45)
Ever	2113 (67)	1461 (70)	652 (62)	2779 (54)
Smoking intensity (%)				
<10 pack-years	638 (20)	421 (20)	217 (21)	1095 (21)
10–19 pack-years	535 (17)	379 (18)	156 (15)	642 (13)
≥20 pack-years	715 (23)	531 (25)	184 (17)	682 (13)
University degree (%)	807 (26)	528 (25)	279 (26)	1768 (34)
Drinking alcohol (%)				
Non-drinkers	260 (8)	177 (8)	83 (8)	291 (6)
Low	1618 (51)	1092 (52)	526 (50)	2282 (44)
Moderate	743 (24)	480 (23)	263 (25)	1287 (25)
High	513 (16)	330 (16)	183 (17)	1202 (23)
Silica exposed (%)	147 (5)	99 (5)	48 (5)	162 (3)
Work status at baseline (%)				
Working	2377 (75)	1604 (77)	773 (73)	4023 (78)
Not working	645 (20)	401 (19)	244 (23)	811 (16)
Missing information*	128 (4)	89 (4)	39 (4)	296 (6)
Work status 5 years before baseline (%)				
Working	2895 (92)	1920 (92)	975 (92)	4591 (89)
Not working	129 (4)	87 (4)	42 (4)	242 (5)
Missing information*	126 (4)	87 (4)	39 (4)	297 (6)

Missing with <2% was not shown.
One pack-year of smoking is equivalent to smoking 20 cigarettes per day for 1 year; alcohol consumption was measured in drinks/week (1 drink=16 g) and categorised based on the alcohol consumption distribution of the controls.
Low (≤median), moderate (≥median and ≤75th centile), high (≥75th centile).
*These are individuals with missing information on occupational physical workload exposures.
ACPA, anticitrullinated protein antibody; BMI, body mass index; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; RA, rheumatoid arthritis.

All analyses were conducted using the SAS software package, V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

In total, data from 3150 cases and 5130 controls were analysed. Among the cases, 66% were ACPA-positive. More RA cases were smokers compared with controls. The characteristics of the participating cases and controls are shown in table 2.

PW as a risk factor for RA

Except for precision work, each of the exposures was associated with an increased risk of developing RA (table 3). Exposed groups had 1.3-fold (95% CI 1.1 to 1.4) to 1.8-fold (95% CI 1.6 to 2.0) higher risk of developing RA compared with unexposed groups after adjustment for age, sex and residential area. The strongest association (OR 1.8, 95% CI 1.6 to 2.0) was observed among participants exposed to hands above shoulder level. Relatively similar ORs were obtained after adjustment for cigarette smoking, BMI, alcohol consumption, recruitment time period, exposure to silica and university degree (see online supplementary table S2). The ORs associated with exposure to PW were relatively consistent between baseline and 5 years before baseline.

Considering that the association between exposure to PW and RA maybe confounded by unmeasured lifestyle factors, we used three different educational levels (junior high school/vocational school level, senior high school level and university level) as a proxy for lifestyle factors and performed a stratified analysis. Statistically significant increased risks were observed across three different educational strata (see online supplementary table S3). Analysis stratified by occupational classes (manual workers and non-manual employees) was also performed. Statistically significant increased risks were also observed under both strata (see online supplementary table S4).

When hierarchical clustering analysis was performed, repetitive bending/turning was moderately correlated with repetitive hand/finger movements (Jaccard coefficient=0.56), lift or carry more than 10 kg was moderately correlated with repetitive bending/turning (Jaccard coefficient=0.52), and hands above shoulder level and hands below knee level were also moderately correlated

Table 3 Risk of developing of rheumatoid arthritis among participants exposed to prolonged repetitive physical workloads in the EIRA

Types of physical workloads		Baseline		5 years before baseline	
		Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)
Repetitive bending/turning	Unexposed	923/1941	1.0 (ref)	963/2039	1.0 (ref)
	Exposed	1446/2067	1.5 (1.3 to 1.6)	1925/2531	1.6 (1.5 to 1.8)
Repetitive hand/finger movements	Unexposed	678/1351	1.0 (ref)	824/1546	1.0 (ref)
	Exposed	1691/2652	1.3 (1.1 to 1.4)	2060/3020	1.3 (1.2 to 1.4)
Lift or carry more than 10 kg	Unexposed	1274/2418	1.0 (ref)	1284/2496	1.0 (ref)
	Exposed	1095/1585	1.3 (1.2 to 1.5)	1602/2077	1.5 (1.4 to 1.7)
Precision work	Unexposed	2098/3584	1.0 (ref)	2536/4061	1.0 (ref)
	Exposed	265/398	1.1 (1.0 to 1.4)	344/487	1.1 (1.0 to 1.3)
Hands below knee level	Unexposed	1908/3448	1.0 (ref)	2215/3827	1.0 (ref)
	Exposed	456/546	1.5 (1.3 to 1.8)	668/736	1.6 (1.4 to 1.8)
Hands above shoulder level	Unexposed	1802/3331	1.0 (ref)	2028/3675	1.0 (ref)
	Exposed	568/668	1.6 (1.4 to 1.8)	857/893	1.8 (1.6 to 2.0)
Vibration	Unexposed	1993/3492	1.0 (ref)	2353/3927	1.0 (ref)
	Exposed	374/499	1.4 (1.2 to 1.6)	535/634	1.5 (1.3 to 1.8)

*OR adjusted for age (10 strata), sex and residential area; baseline is the year when the participants were diagnosed with rheumatoid arthritis.
EIRA, Epidemiological Investigation of Rheumatoid Arthritis; ref, reference.

(Jaccard coefficient=0.43). Precision work and vibration were found to be relatively different from all other types of PW (data not shown). When different types of PW exposure in this study were considered as potential confounding factors and fitted in the statistical model as a covariate (one at a time), statistically significant ORs were still observed (see online supplementary table S5). When all types of PW were included simultaneously in the statistical model, ORs associated with repetitive bending/turning, repetitive hand/finger movements, lift or carry more than 10 kg and hands above shoulder level remained statistically significant (see online supplementary table S6).

Analyses with each exposure variable as an ordinal variable (ie, with all possible cut-points) were performed. Higher ORs were observed for those who were exposed to PW every day or 2–4 days/week than for those who were exposed to PW almost never/rarely or 1–3 days/month. This observation applies to all types of PW exposure 5 years before baseline except for precision work and vibration (data not shown). These trends were still observed after adjusting for potential confounders (data not shown).

The risk of developing RA increased with increasing number of PW exposures (table 4). The ORs increased from 1.2 (95% CI 1.0 to 1.4) for participants exposed to one of the PW exposures to 3.6 (95% CI 2.8 to 4.8) for participants exposed to all of the six PW exposures (p for trend <0.0001). This trend remained statistically significant (p for trend <0.0001) after adjustment for potential confounding factors.

Table 4 Risk of developing of rheumatoid arthritis across groups exposed to different number of types of prolonged repetitive physical workloads in the EIRA

Number of PW exposures	Cases/controls	OR* (95% CI)	OR† (95% CI)
0	206/520	1.0 (ref)	1.0 (ref)
1	596/1283	1.2 (1.0 to 1.4)	1.1 (0.9 to 1.3)
2	720/1156	1.5 (1.3 to 1.9)	1.5 (1.2 to 1.8)
3	525/706	1.9 (1.5 to 2.3)	1.7 (1.4 to 2.1)
4	328/415	2.1 (1.6 to 2.6)	1.9 (1.5 to 2.4)
5	298/295	2.6 (2.1 to 3.3)	2.4 (1.9 to 3.0)
6	195/153	3.6 (2.8 to 4.8)	3.2 (2.4 to 4.2)
p Value for trend		<0.0001	<0.0001

These are exposures 5 years before baseline.
*OR adjusted for age (10 strata), sex and residential area.
†OR adjusted for age (10 strata), sex, residential area and smoking.
EIRA, Epidemiological Investigation of Rheumatoid Arthritis; PW, physical workload; ref, reference.

PW as a risk factor for RA in relation to ACPA status

When the RA cases were stratified by ACPA status, the ORs observed for ACPA-positive RA ranged from 1.2 (95% CI 1.1 to 1.4) to 1.8 (95% CI 1.6 to 2.0). The ORs observed for ACPA-negative RA (1.4 (95% CI 1.2 to 1.6) to 1.7 (95% CI 1.5 to 2.0)) were relatively similar to the ACPA-positive subgroup, except for precision work (table 5). There was no substantial change in the ORs after adjustment for potential confounders. The ORs observed at baseline and 5 years before baseline were also relatively similar for both subgroups of the disease.

Interaction between PW and *HLA-DRB1* SE in relation to ACPA-positive RA

An increased risk of ACPA-positive RA was found for participants with SE but unexposed to PW, as well as for participants exposed to PW and SE. Significant SE–PW interactions, with AP values ranging from 0.3 (95% CI

Table 5 Risk of developing ACPA-positive RA and ACPA-negative RA among participants exposed to prolonged repetitive physical workload

		ACPA-positive RA				ACPA-negative RA			
		Baseline		5 years before baseline		Baseline		5 years before baseline	
Types of physical workload		Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)
Bending/turning	Unexposed	646/1941	1.0 (ref)	654/2039	1.0 (ref)	277/1941	1.0 (ref)	309/2039	1.0 (ref)
	Exposed	956/2067	1.4 (1.3 to 1.6)	1261/2531	1.6 (1.4 to 1.8)	490/2067	1.6 (1.4 to 1.9)	664/2531	1.7 (1.5 to 2.0)
Repetitive hand/finger movements	Unexposed	471/1351	1.0 (ref)	559/1546	1.0 (ref)	207/1351	1.0 (ref)	265/1546	1.0 (ref)
	Exposed	1129/2652	1.2 (1.1 to 1.4)	1355/3020	1.2 (1.1 to 1.4)	562/2652	1.4 (1.2 to 1.7)	705/3020	1.4 (1.2 to 1.6)
Lift or carry more than 10 kg	Unexposed	865/2418	1.0 (ref)	871/2496	1.0 (ref)	409/2418	1.0 (ref)	413/2496	1.0 (ref)
	Exposed	735/1585	1.3 (1.2 to 1.5)	1043/2077	1.5 (1.3 to 1.7)	360/1585	1.4 (1.2 to 1.6)	559/2077	1.6 (1.4 to 1.9)
Precision work	Unexposed	1428/3584	1.0 (ref)	1702/4061	1.0 (ref)	670/3584	1.0 (ref)	834/4061	1.0 (ref)
	Exposed	169/398	1.1 (0.9 to 1.3)	208/487	1.0 (0.9 to 1.2)	96/398	1.3 (1.0 to 1.7)	136/487	1.4 (1.1 to 1.7)
Hands below knee level	Unexposed	1295/3448	1.0 (ref)	1468/3827	1.0 (ref)	613/3448	1.0 (ref)	747/3827	1.0 (ref)
	Exposed	304/546	1.5 (1.3 to 1.8)	447/736	1.6 (1.4 to 1.9)	152/546	1.6 (1.3 to 1.9)	221/736	1.6 (1.3 to 1.8)
Hands above shoulder level	Unexposed	1225/3331	1.0 (ref)	1346/3675	1.0 (ref)	577/3331	1.0 (ref)	682/3675	1.0 (ref)
	Exposed	375/668	1.6 (1.4 to 1.8)	567/893	1.8 (1.6 to 2.0)	193/668	1.7 (1.4 to 2.0)	290/893	1.7 (1.5 to 2.0)
Vibration	Unexposed	1357/3492	1.0 (ref)	1571/3927	1.0 (ref)	636/3492	1.0 (ref)	782/3927	1.0 (ref)
	Exposed	242/499	1.3 (1.1 to 1.6)	344/634	1.5 (1.3 to 1.8)	132/499	1.5 (1.2 to 1.9)	191/634	1.6 (1.3 to 1.9)

*OR adjusted for age (10 strata), sex and residential area; baseline is the year when the participants were diagnosed with RA.
ACPA, anticitrullinated protein antibody; RA, rheumatoid arthritis; ref; reference.

0.1 to 0.5) to 0.4 (95% CI 0.2 to 0.6) were observed for all PWs (table 6), except for precision work and vibration.

Among those without *HLA-DRB1* SE, the association between different PWs and ACPA-positive RA was statistically non-significant (table 6).

DISCUSSION

In this population-based case–control study, we found that some prolonged repetitive PW, such as repetitive bending/turning, repetitive hand/finger movements, lift or carry more than 10 kg, hands below knee level, hands above shoulder level and vibration are associated with an increased risk of RA. The increased risk is relatively similar between ACPA-positive and ACPA-negative RA. Furthermore, we found that an increasing risk of RA is associated with increasing number of types of PW exposure. Significant interactions between PW and *HLA-DRB1* SE are found for the risk of ACPA-positive RA for all studied PWs except for precision work and vibrations.

A small case–control study conducted in Sweden reported an association between occupational exposure to vibration and risk of RA among men.[30] Studies on the association of other types of prolonged repetitive PW and risk of RA have not been reported before. To the best of our knowledge, this is the first population-based case–control study that systematically studied the association of PWs and risk of RA.

This is a population-based case–control study that included incident RA cases in defined areas of Sweden. The cases were given the questionnaires at the time when they were diagnosed with RA. Matched controls were randomly chosen in concomitant with the inclusion of the case. The response rate is high with 94% for cases and 77% for controls, which decreases the magnitude of potential selection bias.

The exposure information was collected retrospectively; consequently, recall bias maybe present in this study. If cases think that PW caused their disease and report it differently from the controls, this may lead to overestimation of the observed results. While there is a possibility that cases may report higher intensity or frequency of exposure to PW than the controls, it is less likely that cases would over-report their exposure status (ie, exposed vs unexposed). This is possibly more likely to be the case for the exposure occurring at baseline. Since our study used questions concerning the situation 5 years before inclusion and used binary exposure variables instead of ordinal exposure variables, such recall bias is minimised and is unlikely to result in a substantial overestimation of the observed ORs.

Pain and fatigue may precede the development of synovitis and the diagnosis of RA.[31] Participants with these symptoms may reduce their exposure to PW; consequently, the number of exposed individuals in the RA group maybe decreased, with regard to the reports on exposure in the year of RA diagnosis (ie, baseline year).

Table 6 Risk of developing ACPA-positive RA among participants exposed to prolonged repetitive physical workload and SE genes in the EIRA

		5 years before baseline			
		HLA-DRB1 SE negative		*HLA-DRB1* SE positive	
Types of physical workloads		**Cases/controls**	**OR* (95% CI)**	**Cases/controls**	**OR* (95% CI)**
Repetitive bending/turning	Unexposed	89/356	1.0 (ref)	391/357	4.4 (3.3 to 5.7)
	Exposed	136/469	1.2 (0.9 to 1.6)	811/485	6.9 (5.3 to 9.0)
	AP				0.3 (0.2 to 0.5)
Repetitive hand/finger movements	Unexposed	79/282	1.0 (ref)	348/298	4.2 (3.1 to 5.6)
	Exposed	146/543	1.0 (0.7 to 1.3)	853/542	5.7 (4.3 to 7.5)
	AP				0.3 (0.1 to 0.4)
Lift or carry more than 10 kg	Unexposed	116/437	1.0 (ref)	539/451	4.6 (3.6 to 5.8)
	Exposed	109/388	1.1 (0.8 to 1.4)	662/390	6.4 (5.0 to 8.2)
	AP				0.3 (0.1 to 0.4)
Precision work	Unexposed	202/731	1.0 (ref)	1068/747	5.3 (4.4 to 6.3)
	Exposed	22/92	0.9 (0.5 to 1.4)	131/92	5.1 (3.7 to 7.0)
	AP				0.0 (−0.3 to 0.3)
Hands below knee level	Unexposed	179/690	1.0 (ref)	925/711	5.1 (4.2 to 6.2)
	Exposed	46/134	1.4 (0.9 to 2.0)	276/130	8.5 (6.4 to 11.1)
	AP				0.4 (0.2 to 0.5)
Hands above shoulder level	Unexposed	170/669	1.0 (ref)	839/675	5.0 (4.1 to 6.1)
	Exposed	55/154	1.5 (1.0 to 2.1)	359/167	8.9 (6.9 to 11.5)
	AP				0.4 (0.3 to 0.5)
Vibration	Unexposed	194/710	1.0 (ref)	980/714	5.1 (4.2 to 6.1)
	Exposed	31/114	1.0 (0.6 to 1.6)	221/125	6.8 (5.1 to 9.1)
	AP				0.3 (0.0 to 0.5)

Baseline is the year when the participants were diagnosed with RA.
Values are OR and 95% CI as compared with unexposed and no SE reference group.
*OR adjusted for age (10 strata), sex and residential area.
ACPA, anticitrullinated protein antibody; AP, attributable proportion due to interaction; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; RA, rheumatoid arthritis; ref, reference; SE, shared epitope.

However, results from analyses of exposures 5 years before and during the year of diagnosis are quite consistent. The proportion of participants that reported the same exposure status 5 years before baseline and at baseline, ranged from 88% to 97% among the cases, and ranged from 90% to 97% among the controls, implying that early RA symptoms had not substantially altered the occupational condition of the cases. Since we used the information on PW 5 years prior to disease onset, the probability that subclinical RA would have affected the experience of workload is minimised. Furthermore, the questions focused on the frequency of different tasks/postures and not the experience of workload. Therefore, such potential bias is not a major problem for the analysis, and any such bias is unlikely to result in overestimation of the strength of association between PW and RA risk.

If participation in the study is related to PW among the controls (ie, those with high workload participate less), this may result in selection bias. Consequently, the observed strength of association between PW and RA risk could be overestimated. According to a previous methodological study that compared registry data between participating and non-participating cases and controls, participation was related to socioeconomic status among both cases and controls, and it was concluded that this only marginally biased the exposure–disease associations in the EIRA.[23] We made a stratified analysis on educational background and similar associations between PW and risk of RA were observed among different strata, which further strengthen the notion that our results are not to a large extent due to selection bias.

PWs are considered as ergonomic hazards which include factors like awkward work postures, repetitive/forceful movements and vibration. These factors usually inflict injuries to several body parts simultaneously, leading to various work-related musculoskeletal disorders or repetitive strain injuries.[32] Studies suggest that these factors generally work in combination in causing work-related musculoskeletal disorders or repetitive strain injuries.[33 34] In this study, we observed that the risk of RA increases with increasing number of types of PW exposed at work. It remains elusive whether the risk of RA conferred by different types of PW is due to a common biological mechanism or different biological mechanisms.

Joints and synovia are consistently exposed to internal physiological and mechanical stress such as fluid/blood flow and external mechanical stress such as PW. While mechanical factors are essential in maintaining the health of normal joint tissues, excessive mechanical

stress may trigger stress signals in the cells of the joints.[35] These stress signals may lead to several changes in the cells and proteins of the exposed tissues, which may eventually lead to the formation of neoepitopes that can be recognised by the immune system.[36]

CONCLUSION

In summary, this study identifies prolonged repetitive PW as a novel environmental factor associated with an increased risk of RA. Exposure to PW was observed to be associated with both ACPA-positive and ACPA-negative RA. Furthermore, gene–environment interaction between SE and PW maybe involved in the aetiology of ACPA-positive RA.

Author affiliations
[1]Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden
[2]Rheumatology Unit, Department of Medicine at Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden
[3]Center for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden

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Contributors PZ carried out data analysis, created the tables and wrote the manuscript. CB initiated the study, provided supervision in data analysis and revised the manuscript. LA and LK are principal investigators of the EIRA study and have been involved in study conception and design, acquisition of data, analysis and interpretation of data as well as manuscript revision.

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