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

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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 involving incident cases of RA (3150 cases and 5130 controls) was gathered. Anticitrullinated protein antibody (ACPA) status of cases was identified. For each PW exposure, exposed participants were compared with unexposed participants. ORs with 95% CIs of RA (overall), ACPA-positive RA and ACPA-negative RA were estimated using logistic regression. PW-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.

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,¹⁰–¹⁵ 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 (90%) 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
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).

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.

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. 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.

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.

Potential confounding factors

Age, residential area, sex, body mass index (BMI <25 or ≥25 kg/m²), 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.

Antibody assays and genotyping

ACPA was measured from the blood samples using enzyme-linked immunosorbent anti-CCP2 assay (Immunoscan ACRA, Epidemiological Investigation of Rheumatoid Arthritis. The positivity cut-off value was 25 units/mL.

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

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All analyses were conducted using the SAS software package, V9.4 (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 2 Characteristics of participating cases and controls in the EIRA

|                  | 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 (%) |                |                             |                             |                  |
| 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 (%) |                    |                             |                             |                  |
| Working          | 2377 (75)           | 1604 (77)                   | 773 (73)                    | 4023 (78)        |
| Not working      | 645 (20)            | 401 (19)                    | 244 (23)                    | 811 (16)         |
| Missing information* |            | 89 (4)                      | 39 (4)                      | 296 (6)          |
| Work status at baseline (%) |          |                             |                             |                  |
| Working          | 2895 (92)           | 1920 (92)                   | 975 (92)                    | 4591 (89)        |
| Not working      | 129 (4)             | 87 (4)                      | 42 (4)                      | 242 (5)          |
| Missing information* |            | 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.
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.

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

| Types of physical workloads       | Baseline Unexposed | Baseline Exposed | 5 years before baseline Unexposed | 5 years before baseline Exposed |
|-----------------------------------|--------------------|------------------|-----------------------------------|---------------------------------|
| Repetitive bending/turning        | 923/1941           | 1446/2067        | 1.0 (ref)                         | 963/2039                        |
| Repetitive hand/finger movements  | 678/1351           | 1691/2652        | 1.0 (ref)                         | 825/1546                        |
| Lift or carry more than 10 kg     | 1274/2418          | 1095/1585        | 1.0 (ref)                         | 1620/2077                       |
| Precision work                    | 2098/3584          | 265/398          | 1.0 (ref)                         | 2356/4061                       |
| Hands below knee level            | 1908/3448          | 456/546          | 1.0 (ref)                         | 668/736                         |
| Hands above shoulder level        | 1802/3331          | 568/668          | 1.0 (ref)                         | 857/893                         |
| Vibration                         | 1993/3492          | 374/499          | 1.0 (ref)                         | 535/634                         |

OR adjusted for age (10 strata), sex and residential area. *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.

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 cases 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.

(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 work and vibration (data not shown). These trends were still observed after adjusting for potential confounders (data not shown).

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

| Types of physical workload                  | Baseline cases/controls | OR (95% CI) | 5 years before baseline cases/controls | OR (95% CI) |
|--------------------------------------------|-------------------------|-------------|----------------------------------------|-------------|
| Bending/turning                            | Unexposed               | 646/1941    | 1.0 (ref)                              | 309/2039    |
|                                           | Exposed                 | 956/2067    | 1.4 (1.3 to 1.6)                       | 1261/2531   |
| Repetitive hand/finger movements           | Unexposed               | 471/1351    | 1.0 (ref)                              | 559/1546    |
|                                           | Exposed                 | 1129/2652   | 1.2 (1.1 to 1.4)                       | 1355/3020   |
| Lift or carry more than 10 kg              | Unexposed               | 865/2418    | 1.0 (ref)                              | 1043/2467   |
|                                           | Exposed                 | 735/1585    | 1.3 (1.2 to 1.5)                       | 562/2652    |
| Precision work                             | Unexposed               | 1428/3584   | 1.0 (ref)                              | 1702/4061   |
|                                           | Exposed                 | 169/398     | 1.1 (0.9 to 1.3)                       | 208/487     |
| Hands below knee level                     | Unexposed               | 1295/3448   | 1.0 (ref)                              | 1456/3757   |
|                                           | Exposed                 | 304/546     | 1.5 (1.3 to 1.8)                       | 447/736     |
| Hands above shoulder level                 | Unexposed               | 1225/3331   | 1.0 (ref)                              | 1346/3975   |
|                                           | Exposed                 | 375/668     | 1.6 (1.4 to 1.8)                       | 567/893     |
| Vibration                                  | Unexposed               | 1357/3492   | 1.0 (ref)                              | 1571/3927   |
|                                           | Exposed                 | 242/499     | 1.3 (1.1 to 1.6)                       | 344/634     |

*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.

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 increased 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 vibration.

A small case–control study conducted in Sweden reported an association between occupational exposure to vibration and risk of RA among men. 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 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 under-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. Participants with these symptoms may reduce their exposure to PW; consequently, the number of exposed individuals in the RA group may decrease, with regard to the reports on exposure in the year of RA diagnosis (ie, baseline year).
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.

PWs are considered as ergonomic hazards which include factors like awkward work postures, repetitive/forceful movements and vibration. These factors usually result in injuries to several body parts simultaneously, leading to various work-related musculoskeletal disorders or repetitive strain injuries. Studies suggest that these factors generally work in combination in causing work-related musculoskeletal disorders or repetitive strain injuries. 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.

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

| Types of physical workloads       | 5 years before baseline | HLA-DRB1 SE negative |          |          |          |
|----------------------------------|-------------------------|----------------------|----------|----------|----------|
|                                  | 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                      | 348/298              | 1.0 (0.7 to 1.3) | 853/542  | 5.7 (4.3 to 7.5) |
| Repetitive hand/finger movements | Unexposed               | 79/282               | 1.0 (ref) | 539/451  | 4.6 (3.6 to 5.8) |
|                                  | Exposed                 | 146/543              | 1.1 (0.8 to 1.4) | 662/390  | 6.4 (5.0 to 8.2) |
|                                  | AP                      | 116/437              | 1.0 (ref) | 353/415  | 5.3 (4.4 to 6.3) |
| Lift or carry more than 10 kg    | Unexposed               | 109/388              | 0.9 (0.5 to 1.5) | 853/542  | 6.4 (5.0 to 8.2) |
|                                  | Exposed                 | 22/92                | 1.0 (ref) | 276/130  | 5.1 (3.7 to 7.0) |
|                                  | AP                      | 202/731              | 1.0 (ref) | 131/92   | 0.0 (−0.3 to 0.3) |
| Precision work                   | 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                      | 170/669              | 1.0 (ref) | 839/675  | 5.0 (4.1 to 6.1) |
| Hands below knee level           | Unexposed               | 55/154               | 1.5 (1.0 to 2.1) | 359/167  | 8.9 (6.9 to 11.5) |
|                                  | Exposed                 | 194/710              | 1.0 (ref) | 980/714  | 5.1 (4.2 to 6.1) |
|                                  | AP                      | 31/114               | 1.0 (0.6 to 1.6) | 221/125  | 6.8 (5.1 to 9.1) |
| Hands above shoulder level       | Unexposed               | 170/669              | 1.0 (ref) | 980/714  | 5.1 (4.2 to 6.1) |
|                                  | Exposed                 | 170/669              | 1.0 (ref) | 980/714  | 5.1 (4.2 to 6.1) |
| Vibration                        | Unexposed               | 170/669              | 1.0 (ref) | 980/714  | 5.1 (4.2 to 6.1) |
|                                  | Exposed                 | 170/669              | 1.0 (ref) | 980/714  | 5.1 (4.2 to 6.1) |

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.

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stress may trigger stress signals in the cells of the joints. 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.

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.

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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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