

ORIGINAL ARTICLE

Working in cold environment and risk of developing rheumatoid arthritis: results from the Swedish EIRA case-control study

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ABSTRACT

Objectives To investigate (1) whether working in cold environment (WCE) is associated with an increased risk of developing rheumatoid arthritis (RA) (overall), anticitrullinated protein antibody (ACPA)-positive RA and ACPA-negative RA and (2) whether WCE interacts with occupational physical workload in conferring RA risk.

Methods Data from the Swedish population-based case-control study Epidemiological Investigation of Rheumatoid Arthritis involving 3659 incident cases and 5925 controls were analysed. Study participants were asked whether they had ever worked in cold/outdoor environment along with their exposure duration and frequency. Occurrence of RA among exposed and unexposed subjects were compared by calculating ORs with 95% CI using logistic regression. Additive interactions between WCE and six types of physical workload were assessed using the principle of departure from additivity by calculating attributable proportion due to interaction (AP).

Results The OR associated with having ever worked in cold environment was 1.5 (95% CI 1.4 to 1.7) for RA (overall), 1.6 (95% CI 1.4 to 1.8) for ACPA-positive RA and 1.4 (95% CI 1.2 to 1.6) for ACPA-negative RA. The risk of developing RA increased with increasing cumulative dose of working in cold indoor environment (p value <0.001), but not working in cold outdoor environment. Positive additive interaction was observed between WCE and repetitive hand/finger movements (AP 0.3 (95% CI 0.1 to 0.5)).

Conclusions WCE is associated with increased risk of developing both ACPA-positive and ACPA-negative RA. A dose-response relationship was found between working in cold indoor environment and risk of developing RA. Moderate additive interaction was observed between exposure to cold environment and exposure to repetitive hand/finger movements.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by synovitis of the joints, which may lead to cartilage and bone destruction and eventually disabilities. It is a systemic heterogeneous disease with various clinical manifestations and comorbidities. Both genetic and environmental risk factors play a role in the aetiology of this

Key messages**What is already known about this subject?**

- Whether exposure to a cold work environment is associated with the risk of developing rheumatoid arthritis is a question that clinicians often receive from patients with rheumatoid arthritis.
- Research that aimed to address such commonly asked question is relatively scarce in the literature.

What does this study add?

- In this study, we observed a positive association between exposure to cold work environment (self-reported) and risk of rheumatoid arthritis.

How might this impact on clinical practice?

- These findings, if further studied and confirmed, may contribute to the understanding of the disease aetiology, may provide an answer to a question that perplexed patients with rheumatoid arthritis and may have an impact on rheumatoid arthritis prevention.

complex disease. One of the environmental factors that has been suspected for centuries to be linked to RA is exposure to cold environment including exposure to cold air, contact with cold surfaces or water immersion.¹ Some patients with RA claim that their disease symptoms, particularly sensitivity to pain and joint stiffness, are influenced or even caused by cold temperature, and some clinical and experimental studies have reported an association between RA disease symptoms and exposure to cold temperature or seasonal changes.²⁻⁴ However, scientific evidence providing an insight on whether exposure to cold environment increases RA risk in healthy individuals is hitherto unavailable. In this study, we used self-reported information on work environment conditions to investigate whether there is an association between working in cold indoor/cold outdoor environment and risk of developing RA (overall), anticitrullinated



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protein antibody (ACPA)-positive RA and ACPA-negative RA. Since working in cold environment is often accompanied with exposure to occupational physical workload, we also investigated the additive interaction between these two occupational exposures with regards to the risk of developing RA.

SUBJECTS AND METHODS

The Epidemiological Investigation of Rheumatoid Arthritis (EIRA) is a population-based case-control study involving incident cases of RA recruited from a defined geographical area in the middle and southern part of Sweden. The subjects, aged 18 years and above, were recruited between 1996 and 2014. The cases were ascertained based on the American College of Rheumatology (ACR)-1987 or ACR-2010 criteria.^{5,6} Controls were selected randomly from the national population register and were frequency matched with the cases on age, sex and residential area. From 1996 to 2006, each case was matched with one control. From 2006 onwards, each case was matched with two controls. If a potential case selected was later excluded due to not fulfilling both ACR-1987 and ACR-2010 criteria, his/her corresponding controls were retained in the study. Details of the study were described in a previous publication.⁷ In total, 3973 cases and 7681 controls were invited to the study, of which, 3724 (94%) cases and 5935 (77%) controls responded by answering the questionnaire. Blood samples from 3680 (99%) participating cases were collected. A total of 44 cases (1% of participating cases) with missing ACPA status were excluded.

Informed consent was received from all participants. This study was approved by the ethics committee of the Karolinska Institute.

Antibody assays

For subclassification of the cases, the presence of ACPAs in the blood samples were measured using the Immunoscan-RA Mark2 ELISA test (Euro-Diagnostica, Malmö, Sweden). The cut-off value for ACPA-positive RA was 25 U/mL.

Exposures

In the questionnaire (see online supplementary file 1), participants were asked whether they: (1) worked in the cold (yes or no) and (2) worked outdoor (yes or no). If they answered 'yes', they may indicate two time periods (from which year to which year) and may also indicate the intensity (hours/week) for each corresponding time period. Those who answered 'yes' in the first question (ie, worked in cold) and 'no' in the second question (ie, worked outdoor) were defined as being exposed to cold indoor work. A subject is defined as being exposed to cold outdoor work if he/she answered 'yes' for both question 1 and question 2 and the time period of working outdoor coincides with the time period of working in cold environment.

Only exposure up to the year when the first disease symptom appeared (index year) was considered. The controls were assigned the same index year as their corresponding cases. A total of 31 subjects (21 cases (0.6%) and 10 controls (0.2%)) were excluded, because their first year of exposure to cold work environment was the same as their index year. The mean time between the appearance of first disease symptom and inclusion in the study was 10 months. Subjects who reported they were still working in the cold at index year were defined as currently exposed, whereas those who reported they worked in the cold prior to index year but not at index year were defined as past exposed. Subjects that were either current or past exposed were defined as ever exposed.

Exposure to occupational physical workloads was assessed based on seven questions about different work postures and movements (see online supplementary file). Participants were asked whether they were exposed to certain types of occupational physical workload (*bending/turning, repetitive hand/finger movements, lift or carry more than 10 kg, prolonged repetitive placing of hands above shoulder level or below knee level and vibration*) at baseline (the time when they answered the questionnaire) and 5 years before baseline. Subjects who reported 'none', 'never or rarely' or 'not at all' were categorised as unexposed to the type of physical workload referred to in the question, whereas subject who gave all other answers were considered as exposed. Subjects who reported they were not working 5 years before baseline were excluded from the physical workload-cold environment interaction analysis.

Potential confounders

The following were considered as potential confounding factors: age (10 strata), residential area (six strata), sex, recruitment time period (1996–2006 and 2006–2014), body mass index (BMI; $<25 \text{ kg/m}^2$ or $\geq 25 \text{ kg/m}^2$), cigarette smoking (<10 pack-years, 10–19 pack-years and ≥ 20 pack-year; one pack-year is equivalent to smoking 20 cigarettes per day for 1 year), educational level (university degree, yes or no), alcohol consumption (non-drinkers, low, moderate and high), silica exposure (rock-drilling, stone crushing or stone dust, yes or no), occupational classes (manual workers and non-manual employees; based on the socioeconomic classification system of Statistics Sweden) and occupational physical workloads (*bending/turning, repetitive hand/finger movements, lift or carry more than 10 kg, placing of hands above shoulder level or below knee level and vibration*).

Statistical analyses

To assess the association between working in cold environment and risk of developing RA (overall), ACPA-positive RA and ACPA-negative RA, ORs with 95% CIs were calculated using logistic regression models. Subjects classified as ever, current or past exposed were compared with subjects that reported they had never been exposed to cold work environment (reference group). Both matched and unmatched analyses were performed and relatively

similar results were obtained. Since higher precision (ie, narrower CI) was attained using the unmatched analysis with adjustment for the matching variables, especially in the analyses related to RA subtypes, we only show the results from the unmatched analyses. The matching variables (age, sex and residential area) and the recruitment time period (1996–2006 and 2006–2014) were included as covariates in all analyses.

Tests of trends (*p* value for trend) were calculated by treating the levels of exposures as a continuous ordinal variable in the logistic regression model. A *p* value of <0.05 was considered statistically significant. Cumulative dose (duration multiplied by intensity) was expressed as work-years. One work-year is equivalent to 2080 hours.

Interactions between exposure to cold work environment and different occupational physical workload exposures were evaluated using the principle of departure from additivity of effect by calculating the attributable proportion due to interaction (AP) value.⁸ AP is the proportion of the incidence among individuals exposed to two interacting factors that is attributable to the interaction per se; thus, an AP greater than 0 indicates presence of interaction. Another way to describe the presence of interaction between two factors is that the effect of one factor on disease risk is modified by the second factor (on additive scale).

All analyses were performed using the SAS software package, V.9.4.

RESULTS

The characteristics of the study population were shown in online supplementary table 1. In total, data from 3659 RA cases and 5925 controls were analysed. Among the cases, 65.6% were ACPA positive and 34.4% were ACPA negative. Among the cases, 23.3% reported that they worked in the cold, 18.0% reported they worked in the cold outdoor and 4.8% reported they worked in the cold indoor. In comparison, among the controls, the proportions who reported they worked in the cold, in the cold outdoor and in the cold indoor were 17.3%, 13.6% and 3.0%, respectively.

Exposure to cold work environment and risk of RA (overall)

When compared with subjects who reported having never worked in cold environment (reference group), the OR of developing RA was 1.5 (95% CI 1.4 to 1.7) among those who had ever worked in cold environment. When the exposure was stratified into cold outdoor and cold indoor environment, the ORs of developing RA were 1.5 (95% CI 1.3 to 1.7) and 1.7 (95% CI 1.4 to 2.1), respectively. For cold outdoor work, relatively similar ORs were observed among current and past exposed groups, whereas for cold indoor work, the OR associated with current exposure (OR 2.3; 95% CI 1.6 to 3.4) was higher than past exposure (OR 1.5; 95% CI 1.2 to 2.0) (*p* for trend <0.001) (table 1). These results did not change substantially after adjusting for cigarette smoking, alcohol consumption, educational level, BMI, silica exposure, occupational class and occupational physical workloads (data not shown).

Table 1 ORs of developing RA (overall), ACPA-positive RA and ACPA-negative RA for subjects worked in the cold, in cold outdoor and cold indoor environment

Exposure status	RA (overall)		ACPA-positive RA		ACPA-negative RA	
	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)
Unexposed	2783/4815	1.0 (ref.)	1811/4815	1.0 (ref.)	972/4815	1.0 (ref.)
Cold*						
Ever	853/1023	1.5 (1.4 to 1.7)	574/1023	1.6 (1.4 to 1.8)	279/1023	1.4 (1.2 to 1.6)
Current	354/392	1.6 (1.4 to 1.9)	236/392	1.7 (1.4 to 2.0)	118/392	1.5 (1.2 to 1.9)
Past	499/631	1.4 (1.3 to 1.7)	338/631	1.5 (1.3 to 1.8)	161/631	1.3 (1.0 to 1.5)
Cold outdoor†						
Ever	658/805	1.5 (1.3 to 1.7)	435/805	1.5 (1.3 to 1.7)	223/805	1.4 (1.1 to 1.6)
Current	289/339	1.5 (1.3 to 1.8)	188/339	1.5 (1.2 to 1.8)	101/339	1.5 (1.2 to 1.9)
Past	369/466	1.4 (1.2 to 1.7)	247/466	1.5 (1.3 to 1.8)	122/466	1.3 (1.0 to 1.6)
Cold indoor†						
Ever	175/177	1.7 (1.4 to 2.1)	125/177	1.9 (1.5 to 2.4)	50/177	1.4 (1.0 to 1.9)
Current	60/47	2.3 (1.6 to 3.4)	46/47	2.8 (1.8 to 4.2)	14/47	1.5 (0.8 to 2.8)
Past	115/130	1.5 (1.2 to 2.0)	79/130	1.6 (1.2 to 2.1)	36/130	1.4 (0.9 to 2.0)

*Missing information on 23 (0.6%) cases and 87 (1.5%) controls.

†Missing information on 43 (1.2%) cases and 128 (2.2%) controls.

ACPA, anticitrullinated protein antibody; RA, rheumatoid arthritis.

OR adjusted for age (10 strata) sex, residential area and recruitment time period (1996–2006 and 2006–2014).

Exposure to cold work environment and risk of ACPA-positive and ACPA-negative RA

For subjects who were exposed to cold work environment, the OR of developing ACPA-positive RA was 1.6 (95% CI 1.4 to 1.8) and the OR of developing ACPA-negative RA was 1.4 (95% CI 1.2 to 1.6). Both exposure to cold indoor work and cold outdoor work were associated with an increased risk of developing ACPA-positive and ACPA-negative RA. However, the increased risk observed for ACPA-negative RA among those who were exposed to cold indoor work was statistically not significant (table 1). When the association between exposure to cold work environment and risk of developing ACPA-positive RA and ACPA-negative RA was investigated separately for men and women, we observed an increased risk for ACPA-positive RA but not ACPA-negative RA among women, and an increased risk for both ACPA-positive and ACPA-negative RA among men (data not shown). These results were not substantially altered after adjustment for potential confounding factors considered (data not shown).

Dose–response relationship between working in cold indoor environment and risk of RA

The risk of developing RA (overall) increased with increasing duration (number of years), intensity (hours/week) and cumulative dose (work-years) of working in cold indoor environment (table 2). The OR of RA increased from 1.2 (95% CI 0.9 to 1.7) for subjects with a cumulative dose of less than 5 work-years to 2.4 (95% CI 1.3 to 4.6) for subjects with a cumulative dose of 10 work-years or more (p for trend <0.001) (table 2). The OR for RA decreased from 1.6 (95% CI 1.1 to 2.5) to 1.2 (95% CI 0.7 to 2.0) after ceased working in cold indoor environment for around 10 years or more (p for trend, 0.023) (table 2). These observed trends were robust across different cut-off values used for categorising number of years for duration and cessation, number of hours/week for intensity and number of work-years for cumulative dose (data not shown). The cut-off values used were: arbitrary cut-off values, median or tertile values among the exposed controls.

Table 2 ORs of developing RA (overall) for subjects worked in cold indoor by duration, intensity, cumulative dose and cessation

Duration (number of years)	Cases/controls	OR* (95% CI)	OR† (95% CI)
Unexposed	2783/4815	1.0 (ref.)	1.0 (ref.)
<10	85/98	1.5 (1.1 to 2.0)	1.3 (0.9 to 1.8)
10–19	45/46	1.7 (1.1 to 2.5)	1.5 (0.9 to 2.4)
≥20	43/31	2.5 (1.5 to 4.0)	2.0 (1.2 to 3.4)
p for trend		<0.001	<0.001
Intensity (hours/week)			
Unexposed	2783/4815	1.0 (ref.)	1.0 (ref.)
<10	52/74	1.2 (0.9 to 1.8)	1.0 (0.7 to 1.5)
10–19	27/25	1.9 (1.1 to 3.3)	1.9 (1.1 to 3.6)
≥20	77/64	2.1 (1.5 to 2.9)	1.8 (1.2 to 2.6)
p for trend		<0.001	<0.001
Cumulative dose (work-years)			
Unexposed	2783/4815	1.0 (ref.)	1.0 (ref.)
<5	100/127	1.4 (1.0 to 1.8)	1.2 (0.9 to 1.7)
5–9	27/16	2.8 (1.5 to 5.3)	1.9 (1.0 to 3.9)
≥10	29/18	2.8 (1.5 to 5.1)	2.4 (1.3 to 4.6)
p for trend		<0.001	<0.001
Cessation (number of years)			
Unexposed	2783/4815	1.0 (ref.)	1.0 (ref.)
<10	53/50	1.8 (1.2 to 2.6)	1.6 (1.1 to 2.5)
10–19	33/40	1.3 (0.8 to 2.2)	1.2 (0.7 to 2.0)
≥20	27/38	1.3 (0.8 to 2.1)	1.2 (0.7 to 2.0)
p for trend		0.001	0.023

*OR adjusted for age (10 strata) sex, residential area and recruitment time period (1996–2006 and 2006–2014).

†OR adjusted for age (10 strata) sex, residential area, recruitment time period (1996–2006 and 2006–2014), cigarette smoking, body mass index, alcohol consumption, university education and silica exposure.

Cumulative dose is the product of duration and intensity.

One work-year is equivalent to 2080 hours.

Table 3 ORs of developing RA (overall) among subjects exposed to prolonged repetitive physical workload and cold work environment 5 years before baseline

Physical workload*	Cold work environment						
		Unexposed		Exposed		AP (95% CI)	p Value
	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)			
Bending/turning	Unexposed	804/1799	1.0 (ref.)	84/88	2.1 (1.5 to 2.9)	-0.2 (-0.6 to 0.1)	0.190
	Exposed	1376/1925	1.5 (1.3 to 1.7)	313/339	2.1 (1.7 to 2.5)		
Repetitive hand/finger movements	Unexposed	611/1223	1.0 (ref.)	131/193	1.4 (1.1 to 1.8)	0.3 (0.1 to 0.5)	<0.001
	Exposed	1566/2499	1.3 (1.2 to 1.5)	266/234	2.6 (2.1 to 3.2)		
Carry more than 10 kg	Unexposed	1152/2265	1.0 (ref.)	49/60	1.7 (1.1 to 2.5)	0.0 (-0.4 to 0.3)	0.871
	Exposed	1026/1462	1.4 (1.2 to 1.5)	348/367	2.0 (1.7 to 2.4)		
Hands below knee level	Unexposed	1846/3316	1.0 (ref.)	172/201	1.6 (1.3 to 2.0)	-0.1 (-0.3 to 0.2)	0.687
	Exposed	331/406	1.4 (1.2 to 1.7)	223/224	1.9 (1.6 to 2.4)		
Vibration	Unexposed	1979/3407	1.0 (ref.)	175/211	1.5 (1.2 to 1.8)	0.2 (-0.1 to 0.4)	0.127
	Exposed	202/316	1.2 (1.0 to 1.5)	221/212	2.0 (1.6 to 2.5)		
Hands above shoulder level	Unexposed	1682/3146	1.0 (ref.)	163/216	1.4 (1.0 to 1.8)	0.1 (-0.1 to 0.4)	0.226
	Exposed	495/578	1.5 (1.3 to 1.8)	234/210	2.3 (1.9 to 2.8)		

Baseline is the year when the participants were recruited (ie, at the time when the patients were diagnosed).

*Missing information on 126 (3.4%) cases and 297 (5.0%) controls.

OR adjusted for age (10 strata), sex, residential area and recruitment time period (1996–2006 and 2006–2014).

AP, attributable proportion due to interaction; RA, rheumatoid arthritis.

Statistically significant dose–response relationships (p for trend <0.001) were observed between working in cold indoor environment and risk of ACPA-positive RA, but not between working in cold indoor environment and risk of ACPA-negative RA (data not shown). Similar trend analyses were also done for subjects who were exposed to cold environment or cold outdoor environment, but no significant trends were observed (data not shown).

Additive interaction between exposure to cold work environment and occupational physical workloads

When compared with those who were unexposed to both cold work environment and physical workloads, increased risks of developing RA (overall) were observed among those who were exposed to either one of the exposures (OR ranged from 1.2 (95% CI 1.0 to 1.5) to 2.1 (95% CI 1.5 to 2.9)) as well as among those who were exposed to both exposures (OR ranged from 1.9 (95% CI 1.6 to 2.4) to 2.6 (95% CI 2.1 to 3.2)). Moderate interaction (AP value 0.3 (95% CI 0.1 to 0.5); p value <0.001) was observed between repetitive hand/finger movements and cold work environment (table 3). Since we only collected information on physical workload exposure at two time points (baseline and 5 years prior to baseline), we performed the interaction action

analysis in table 3 with both exposures (physical workload and cold work environment) restricted to 5 years prior to baseline.

Considering that exposures more than 5 years before baseline might also be of importance and to increase the statistical power, an analysis where the time of exposure to cold work environment was not restricted to 5 years before baseline, while exposure to physical workload remained at 5 years before baseline, was also performed. Moderate additive interactions (AP values ranged from 0.2 (95% CI 0.0 to 0.4; p value 0.029) to 0.3 (95% CI 0.1 to 0.4; p value 0.004) between exposure to cold work environment and four types of physical workloads (repetitive hand/finger movements, carry more than 10 kg, placing hands above shoulder level and vibration) were observed (online supplementary table 2).

DISCUSSIONS

Working in cold environment was observed to be associated with an increased risk of developing both ACPA-positive and ACPA-negative RA. A dose–response relationship was observed between working in cold indoor environment and risk of RA (overall). Additive

interactions between exposure to cold work environment and some types of physical workload were observed.

Several epidemiological studies have reported an association between exposure to cold environment and risk of musculoskeletal disorders such as shoulder, lower back or neck pain and white fingers.^{9–11} Our study, to our knowledge, is the first population-based study that investigates the association between working in cold environment and risk of developing RA among healthy individuals.

This study is a population-based study using incident RA cases with a high response rate (94% for cases and 77% for controls), which decrease the magnitude of potential selection bias. Another strength of the study is the possibility of taking many potential confounding factors into account. Nevertheless, the possibility of residual confounding cannot be precluded.

If the non-participating controls are those who tend to work in cold environment, then the observed association between working in cold environment and RA risk could be slightly overestimated. Previous analysis on the non-participating subjects performed using registry data concluded that non-participation was associated with low socioeconomic status.¹² However, the observed positive association is robust across different occupational classes. Based on these background data, we considered that such potential selection bias might have only minor effect on the observed result in this study.

To minimise recall bias and the possibility of reverse causation due to retrospectively collected exposure information, cases were included into the study shortly after their first disease symptom onset (ie, 10 months on average), and only the exposure status prior to disease symptom onset was taken into consideration and analysed. Nevertheless, exposure to cold environment has long been speculated as a risk factor for RA. Hence, recall bias may prevail if cases, who believed that working in cold environment had caused their disease, recalled their exposure differently from the controls. Such recall bias may lead to overestimation of the observed ORs. However, we observed that the occupations of the cases and controls who reported they had ever worked in cold environment were relatively similar (online supplementary table 3). The five most frequent occupations of both controls and cases who reported they worked in the cold were: social work, sales work (goods), building and construction work, metal machine work and agriculture. This may suggest that the impact of recall bias on the results is likely to be of minor magnitude in this study.

The exposure in this study is self-reported. We are unable to give a range of specific temperatures that defines a cold work environment. The definition of a cold environment depends on the subjective judgement and experience of the participants. If cases and controls have different sensitivity to cold temperature, then this could lead to differential misclassification of exposure. However, the most common occupations of those who were exposed to cold indoor environment are within the retail, food processing, package and storage industry

(66%). In these industries, the work environment or products they handle usually have a temperature of $<8^{\circ}\text{C}$ for food safety purposes. In this study, we are also unable to distinguish the effect of cold temperature independently from humidity and barometric pressure as temperature is highly correlated with both humidity and pressure.

This study does not explore the relationship between 'temperature exposure' and risk of RA, instead it investigates 'exposure to the experience of cold work environment (self-reported)' and risk of RA. We do not preclude the possibility that maybe subjective feeling of cold at work is a more relevant risk factor for RA as compared with cold temperature. Furthermore, temperature is only one of the many factors that contribute to the experience of cold work environment. Other possible factors are humidity, barometric pressure and things in the work environment such as ice, water or freezer. Although further studies are needed to identify what exactly is/are the element/s in the cold work environment that is/are associated with risk of RA, this study is valuable for creating aetiological hypotheses. Such hypotheses can serve as basis for conducting interventional studies to investigate causal mechanisms.

A dose–response relationship was observed for cold indoor work exposure but not cold outdoor work exposure. A possible reason might be that outdoor temperature varies according to seasonal and weather changes, whereas indoor temperature is more stable and consistent. People working in cold outdoor environment tend to wear protective clothing against cold weather, for example, gloves, which may render their hands less exposed to cold. Lastly, the effect of cold indoor work and cold outdoor work on human physiological response may be inherently different.

We have previously observed that exposure to six different types of occupational prolonged repetitive physical workloads increases the risk of developing RA.¹³ Considering that working in cold environment may demand higher workload from the muscles, tendons and joints than working under ambient temperature,¹⁴ we performed an interaction analysis between cold work environment exposure and different types of physical workload exposure. A significant additive interaction was observed between working in cold environment and exposure to repetitive hand/finger movements. In other words, the effect due to the simultaneous exposure to the two factors (working in a cold environment and repetitive hand/finger movements) regarding the risk of developing RA is higher than the summation of the independent effect of each of the two factors. This observation indicates a possible mechanistic interaction between these exposures in RA. While there are studies that attempt to delineate the effect of acute/short-term cold exposure on the immune system,^{15–17} studies that investigate the impact of long-term exposure to cold environment in conjunction with high physical workload on the immune system are scarce. Whether exposure to long-term cold work environment causes aberrant

immune reactions resulting into a chronic inflammatory disease like RA remains elusive.

In summary, our study provides support for an association between working in cold environment and risk of developing RA. In addition, additive interaction between working in cold environment and exposure to repetitive hand/finger movements was observed, indicating that both exposures may interact in RA disease aetiology.

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

Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethics committee of the Karolinska Institutet.

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