Occupational physical workload and development of anti-collagen type II antibodies in rheumatoid arthritis: results from the Swedish EIRA population-based case-control study

Sirs,

We previously observed an association between occupational physical workload (PW) and risk of developing rheumatoid arthritis (RA) (1). Antibodies against collagen type II (CII), which are associated with HLA-DRB*01 and *03 (2) are transiently elevated at RA diagnosis but do not appear in the pre-diagnostic stage (3). Movements increase urinary CII fragments in osteoarthritis patients (4) but show variable effect on serum levels in healthy subjects (5-7). As cartilage damage might lead to immune activation and production of anti-CII antibodies, we hypothesised that exposure to PW would associate more strongly with anti-CII positive than with anti-CII negative RA.

Data involving 2916 incident RA cases and 5130 controls (1205 with anti-CII data) from the Swedish Epidemiological Investigations in Rheumatoid Arthritis (EIRA) population-based case-control study were analysed (8). Information on occupational exposure to PW at baseline and five years earlier was collected through questionnaires (Supplementary materials and (1)). Anti-CII levels were analysed with ELISA (2, 9). Genotyping was done using sequence-specific primer-polymerase chain reaction. The odds ratios (OR) with 95% CI of developing anti-CII positive RA or anti-CII negative RA was calculated using logistic regression, after correction for age, sex and residential area. Additional adjustments for educational level, cigarette smoking, alcohol consumption, occupational class, body mass index, recruitment time periods and anti-CII antibody test batches did not significantly change the results and were excluded from the final analyses (Supplementary Table S1).

Anti-CII was detected in 5.3% (155/2116) of patients and 3.0% (36/1205) of controls (*p*=0.0008). The OR observed for the association between different types of PW and anti-CII positive RA ranged from 1.2 (0.8–1.8) to 2.2 (1.5–3.1). The OR for the association between PW and anti-CII negative RA ranged from 1.3 (1.1–1.4) to 1.8 (1.6–2.0). No difference was observed between the OR for anti-CII positive RA and anti-CII negative RA (all *p*-values >0.10; Table I). Moreover, stratification for HLA-DRB*01 and *03 did not yield any statistical differences (Table II).

Strengths of the study include a population-based design with incident cases, high response rate (cases 95%, controls 77%) and the possibility to adjust for numerous potential confounding factors. It is unlikely that from the use of self-reported PW, information will result in substantial overestimation of observed ORs (1). Since anti-CII probably appear close to the time of diagnosis, we speculated that exposure to PW at baseline would be more strongly associated with anti-CII positive RA compared with exposure to PW at 5 years before diagnosis. However, the characteristics of our data hampered the possibility to investigate this hypothesis. Around 59–74% of cases and 62–78% of controls reporting PW 5 years before baseline were also exposed at baseline; 69–78% of cases and 75–83% of controls who reported they were unexposed at 5 years before baseline were also unexposed at baseline. These high proportions indicate that the groups we compared at baseline and 5 years before baseline are almost identical.

In this study, we observed that PW is associated with both anti-CII positive RA and anti-CII negative RA. The magnitude of association between PW and anti-CII positive RA/anti-CII negative RA are relatively similar, which may indicate that PW does not mediate production of anti-CII in early RA. Nevertheless, the null finding remains uncertain and should be interpreted with caution, since our study, although large, might have insufficient power to detect a biologically significant difference.

In conclusion, we found no evidence suggesting an association between PW and elevated anti-CII levels at the time of diagnosis.

P. ZENG[1]
E. PERTSINIDOU[2]
B. BRYNEDAL[1,3]
V.A. MANIVEL[2]
L. KLARESKOG[3]
M. MULLAZEHI[2]
S. SAEVARSDOTTIR[1,3]
C. BENGTSSON[1]
L. ALFREDSSON[1,4]
J. RÖNNELID[2]

Table I. Association between exposure to physical workload and risk of developing anti-CII positive RA and anti-CII negative RA.

Types of physical workload		Anti-CII Positive RA				Anti-CII Negative RA			
		Baseline		Five years before baseline		Baseline		Five years before baseline	
		cases/controls	OR (95%CI)	cases/controls	OR (95%CI)	cases/controls	OR (95%CI)	cases/controls	OR (95%CI)
Repetitive turning/bending	unexposed	40/1940	1.0 (ref.)	40/2039	1.0 (ref.)	805/1940	1.0 (ref.)	849/2039	1.0 (ref.)
	exposed	71/2067	1.7 (1.1-2.5)	105/2531	2.2 (1.5-3.1)	1259/2067	1.5 (1.3-1.6)	1671/2531	1.6 (1.4-1.7)
Repetitive hand/finger movements	unexposed	30/1351	1.0 (ref.)	42/1546	1.0 (ref.)	588/1351	1.0 (ref.)	717/1546	1.0 (ref.)
	exposed	81/2652	1.4 (0.9-2.1)	103/3020	1.2 (0.9-1.8)	1476/2652	1.3 (1.1-1.4)	1800/3020	1.3 (1.2-1.4)
Carry >10kg	unexposed	63/2418	1.0 (ref.)	63/2496	1.0 (ref.)	1108/2418	1.0 (ref.)	1112/2496	1.0 (ref.)
	exposed	48/1585	1.2 (0.8-1.8)	82/2077	1.7 (1.2-2.4)	955/1585	1.3 (1.2-1.5)	1406/2077	1.5 (1.4-1.7)
Hands below knee level	unexposed	93/3448	1.0 (ref.)	110/3827	1.0 (ref.)	1655/3448	1.0 (ref.)	1925/3827	1.0 (ref.)
	exposed	18/546	1.3 (0.8-2.2)	35/736	1.7 (1.2-2.6)	404/546	1.5 (1.3-1.8)	591/736	1.6 (1.4-1.8)
Vibration	unexposed	95/3492	1.0 (ref.)	117/3927	1.0 (ref.)	1723/3492	1.0 (ref.)	2044/3927	1.0 (ref.)
	exposed	16/499	1.4 (0.8-2.5)	28/634	1.8 (1.1-2.9)	339/499	1.4 (1.2-1.7)	477/634	1.6 (1.3-1.8)
Hands above shoulder level	unexposed	87/3331	1.0 (ref.)	101/3675	1.0 (ref.)	1567/3331	1.0 (ref.)	1770/3675	1.0 (ref.)
	exposed	24/668	1.4 (0.9-2.3)	44/893	1.9 (1.3-2.8)	497/668	1.6 (1.4-1.8)	748/893	1.8 (1.6-2.0)

OR adjusted for age, sex and residential area.
Baseline denotes occupational physical workload exposure status at the time of diagnosis. Five years before baseline denotes occupational physical workload status at 5 years prior to diagnosis. OR: odds ratio; anti-CII: anti-collagen type II antibodies; RA: rheumatoid arthritis; 95% CI: 95% confidence interval.

Letters to the Editors

Table II. Association between exposure to physical workload and risk of developing anti-CII positive RA and anti-CII negative RA stratified by HLA-DRB1*01/*03 status.

*Presence of HLA-DRB1*01 or HLA-DRB1*03*

Types of physical workload		Anti-CII Positive RA				Anti-CII Negative RA			
		Baseline		Five years before baseline		Baseline		Five years before baseline	
		cases/ controls	OR (95%CI)	cases/ controls	OR (95%CI)	cases/ controls	OR (95%CI)	cases/ controls	OR (95%CI)
Repetitive turning/bending	unexposed	14/262	1.0 (ref.)	18/303	1.0 (ref.)	233/262	1.0 (ref.)	242/303	1.0 (ref.)
	exposed	35/307	2.2 (1.2-4.2)	49/401	2.1 (1.2-3.8)	374/307	1.4 (1.1-1.8)	523/401	1.7 (1.3-2.1)
Repetitive hand/finger movements	unexposed	14/204	1.0 (ref.)	17/256	1.0 (ref.)	185/204	1.0 (ref.)	224/256	1.0 (ref.)
	exposed	35/363	1.3 (0.7-2.5)	50/446	1.7 (0.9-2.9)	424/363	1.3 (1.0-1.7)	539/446	1.4 (1.1-1.8)
Carry >10kg	unexposed	29/323	1.0 (ref.)	30/358	1.0 (ref.)	328/323	1.0 (ref.)	326/358	1.0 (ref.)
	exposed	20/246	1.0 (0.5-1.8)	37/345	1.4 (0.8-2.3)	280/246	1.0 (0.8-1.3)	436/345	1.3 (1.1-1.6)
Hands below knee level	unexposed	40/490	1.0 (ref.)	48/592	1.0 (ref.)	483/490	1.0 (ref.)	571/592	1.0 (ref.)
	exposed	9/79	1.5 (0.7-3.3)	19/112	2.2 (1.2-4.0)	125/79	1.6 (1.1-2.1)	194/112	1.8 (1.4-2.4)
Vibration	unexposed	40/483	1.0 (ref.)	52/586	1.0 (ref.)	497/483	1.0 (ref.)	607/586	1.0 (ref.)
	exposed	9/84	1.7 (0.7-4.1)	15/116	1.7 (0.8-3.5)	111/84	1.2 (0.8-1.7)	158/116	1.3 (0.9-1.7)
Hands above shoulder level	unexposed	38/468	1.0 (ref.)	46/561	1.0 (ref.)	453/468	1.0 (ref.)	532/561	1.0 (ref.)
	exposed	11/100	1.4 (0.7-3.0)	21/141	1.9 (1.1-3.4)	155/100	1.6 (1.2-2.1)	231/141	1.7 (1.4-2.2)

*Absence of HLA-DRB1*01 or HLA-DRB1*03*

Types of physical workload		cases/ controls	OR (95%CI)	cases/ controls	OR (95%CI)	cases/ controls	OR (95%CI)	cases/ controls	OR (95%CI)
Repetitive turning/bending	unexposed	18/372	1.0 (ref.)	16/408	1.0 (ref.)	337/372	1.0 (ref.)	346/408	1.0 (ref.)
	exposed	20/431	1.0 (0.5-1.9)	30/562	1.4 (0.8-2.7)	551/431	1.4 (1.2-1.7)	728/562	1.5 (1.3-1.8)
Repetitive hand/finger movements	unexposed	12/275	1.0 (ref.)	17/325	1.0 (ref.)	261/275	1.0 (ref.)	311/325	1.0 (ref.)
	exposed	26/527	1.1 (0.6-2.3)	29/645	0.9 (0.5-1.6)	626/527	1.2 (1.0-1.5)	763/645	1.2 (1.0-1.5)
Carry >10kg	unexposed	15/486	1.0 (ref.)	16/532	1.0 (ref.)	473/486	1.0 (ref.)	478/532	1.0 (ref.)
	exposed	23/316	2.3 (1.2-4.6)	30/438	2.4 (1.2-4.4)	413/316	1.3 (1.1-1.6)	597/438	1.5 (1.2-1.8)
Hands below knee level	unexposed	32/694	1.0 (ref.)	37/811	1.0 (ref.)	723/694	1.0 (ref.)	837/811	1.0 (ref.)
	exposed	6/107	1.1 (0.4-2.7)	9/157	1.2 (0.6-2.7)	162/107	1.4 (1.1-1.8)	235/157	1.4 (1.1-1.8)
Vibration	unexposed	33/710	1.0 (ref.)	39/842	1.0 (ref.)	748/710	1.0 (ref.)	881/842	1.0 (ref.)
	exposed	5/90	1.1 (0.4-3.1)	7/126	1.2 (0.5-3.0)	138/90	1.4 (1.0-1.9)	193/126	1.5 (1.1-1.9)
Hands above shoulder level	unexposed	27/682	1.0 (ref.)	30/785	1.0 (ref.)	682/682	1.0 (ref.)	766/785	1.0 (ref.)
	exposed	11/121	2.2 (1.1-4.7)	16/185	2.4 (1.3-4.5)	206/121	1.7 (1.3-2.2)	307/185	1.7 (1.4-2.1)

OR adjusted for age, sex and residential area.
Baseline denotes occupational physical workload exposure status at the time of diagnosis. Five years before baseline denotes occupational physical workload status at 5 years prior to diagnosis. OR: odds ratio; anti-CII: anti-collagen type II antibodies; RA: rheumatoid arthritis; 95% CI: 95% confidence interval.

[1]*Institute of Environmental Medicine, Karolinska Institute, Stockholm;*
[2]*Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala;*
[3]*Rheumatology Unit, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institute, Stockholm;*
[4]*Center for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden.*

Please address correspondence to:
Johan Rönnelid,
Department of Immunology, Genetics and Pathology, Uppsala University, Rudbecklaboratoriet, 75185 Uppsala (Uppland), Sweden.
E-mail: johan.ronnelid@igp.uu.se

References

1. ZENG P, KLARESKOG L, ALFREDSSON L, BENGTSSON C: Physical workload is associated with increased risk of rheumatoid arthritis: results from a Swedish population-based case-control study. *RMD Open* 2017; 3: e000324.
2. MANIVEL VA, MULLAZEHI M, PADYUKOV L *et al.*: Anticollagen type II antibodies are associated with an acute onset rheumatoid arthritis phenotype and prognosticate lower degree of inflammation during 5 years follow-up. *Ann Rheum Dis* 2017; 76: 1529-36.
3. MÖTTÖNEN T, HANNONEN P, OKA M *et al.*: Antibodies against native type II collagen do not precede the clinical onset of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 776-9.
4. HUNT MA, POLLOCK CL, KRAUS VB *et al.*: Relationships amongst osteoarthritis biomarkers, dynamic knee joint load, and exercise: results from a randomized controlled pilot study. *BMC Musculoskelet Disord* 2013; 14: 115.
5. PRUKSAKORN D, TIRANKGURA P, LUEVITOON-VECHKIJ S *et al.*: Changes in the serum cartilage biomarker levels of healthy adults in response to an uphill walk. *Singapore Med J* 2013; 54: 702-8.
6. MUNDERMANN A, KLENK C, BILLICH C *et al.*: Changes in cartilage biomarker levels during a transcontinental multistage footrace over 4486 km. *Am J Sports Med* 2017; 45: 2630-6.
7. VUOLTEENAHO K, LEPPANEN T, KEKKONEN R, KORPELA R, MOILANEN E: Running a marathon induces changes in adipokine levels and in markers of cartilage degradation--novel role for resistin. *PLoS One* 2014; 9: e110481.
8. STOLT P, BENGTSSON C, NORDMARK B *et al.*: Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. *Ann Rheum Dis* 2003; 62: 835-41.
9. MULLAZEHI M, MATHSSON L, LAMPA J, RÖNNE-LID J: High anti-collagen type-II antibody levels and induction of proinflammatory cytokines by anti-collagen antibody-containing immune complexes in vitro characterise a distinct rheumatoid arthritis phenotype associated with acute inflammation at the time of disease onset. *Ann Rheum Dis* 2007; 66: 537-41.