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Social stressors and risk of rheumatoid arthritis and their relationship to known modifiable risk factors: results from the Swedish EIRA study

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Objectives: To investigate whether low social support or low decision latitude at work correlate with risk of rheumatoid arthritis (RA), and whether and how those factors are associated with known modifiable risk factors for RA.
Method: The Swedish population-based EIRA study included, from 1996 to 2015, 3724 incident RA cases and 5935 controls, matched for age, gender, and residential area. Participants filled in detailed questionnaires at diagnosis. Using logistic regression, we investigated whether low social support and low decision latitude at work were associated with RA risk, and whether and how these exposures are associated with known modifiable risk factors for RA.
Results: Low decision latitude at work was associated with RA risk in unadjusted analyses [odd ratio (OR) = 1.52, 95% confidence interval (CI) = 1.20–1.94], but this association was weakened after adjustment for known RA risk factors (adjusted OR = 1.24, 95% CI = 0.93–1.63). Low social support was not associated with RA risk (unadjusted OR = 1.05, 95% CI = 0.95–1.15). Cases reporting low decision latitude were more often smokers (OR = 2.05, 95% CI = 1.33–3.16), without university degrees (OR = 8.23, 95% CI = 5.13–13.22), and more often female (OR = 2.52, 95% CI = 1.66–3.81), with a similar pattern among controls. Cases reporting low social support were more often men (OR = 1.60, 95% CI = 1.40–1.83), smokers (OR = 1.46, 95% CI = 1.26–1.70), obese (OR = 1.29, 95% CI = 1.09–1.54), physically inactive (OR = 2.78, 95% CI = 1.98–3.90), and without university degrees (OR = 2.04, 95% CI = 1.77–2.36), with a similar pattern among controls.
Conclusion: Low decision latitude coexisted with several known environmental/social risk factors for RA, together defining groups of individuals at increased risk of RA. These risk factors should be viewed in context when testing actions to diminish RA risk in prospective studies.

The aetiological background of rheumatoid arthritis (RA) is complex and not fully understood. However, we have an increasing knowledge about modifiable factors associated with increased risk of RA and how some of these factors, such as smoking, may trigger molecular mechanisms leading to joint inflammation in RA (1–3), while the potential causal mechanisms are less well understood for other modifiable risk factors, such as low educational level, obesity, and type of occupation (4–9). Levels of social support and work-related stress have received increasing interest as being associated with the risk of several other chronic diseases, including cardiovascular diseases (10, 11), while data on RA risk are scarce.

For individualized care of patients at risk, including lifestyle recommendations, it is important to understand whether modifiable factors may impact the risk by themselves; that is, whether smoking cessation and weight reduction programmes are the key, or whether related social factors may also affect the risk. Therefore, we investigated in a large population-based study with high coverage, whether low social support in general and/or low decision latitude at work correlate with RA risk. Subsequently, we investigated whether these factors are associated with the presence of already known modifiable risk factors for RA.

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Method

Source population with RA: the Epidemiological Investigation of Rheumatoid Arthritis (EIRA)

EIRA is a population-based case–control study covering the middle and southern parts of Sweden, including RA cases diagnosed by rheumatology specialists within 1 year from symptom onset and fulfilling the American College of Rheumatology (ACR) 1987 criteria for RA (12). During the period 1996–2015, 3724 cases and 5935 controls participated in the study.

For each case, one control was randomly selected from the national population register, matched for age, gender, and residential area. Since 2006, two controls per case were selected by the same method, instead of one. As described in detail elsewhere (13), the study participants answered a detailed questionnaire about socioeconomic conditions and lifestyle habits. The response rate to the study questionnaire was 93% for cases and 73% for the matched controls.

Exposures

Social support outside work at the time of RA diagnosis was obtained by four questions and decision latitude at work was obtained by six questions, as described in Supplementary tables S1 and S2. Information on decision latitude at work was measured according to questions developed by Karasek and Theorell, defined as low level of influence on the working situation, low demands on occupational skills, and low possibility of further education in the workplace (14). Questions on decision latitude at work were only included in the EIRA part 1 questionnaire (years 1996–2006; 1998 cases and 2252 controls), while other exposures, including social support, were included during a longer study period of EIRA (years 1996–2015, 3724 cases and 5935 controls). Incomplete responses from participants were followed up through telephone interviews, yielding a response rate of > 99% for the main exposures.

Other modifiable factors were also captured at diagnosis and classified for the present analysis as follows: university degree (yes/no), smoking habits (current smoking, yes/no), obesity (body mass index > 30 kg/m^2, yes/no), and leisure-time physical inactivity (yes/no).

Rheumatoid factor (RF) status was determined using standard procedures and anti-citrullinated peptide (anti-CCP) antibodies were assessed by the standard enzyme-linked immunosorbent assay (anti-CCP2 assay, Immunoscan-RA Mark 2 ELISA test; Euro-Diagnostica, Malmö, Sweden).

Statistical analysis

For analyses, we dichotomized the main exposures using quartiles; the lowest quartile cut-off among controls was used to define the exposure and was compared to the remaining three quartiles. Low decision latitude was defined, as in a previous report (13), as the lowest quartile compared to the highest quartile.

Flowcharts for the process of defining the exposures are available in Supplementary figures S1 and S2, along with frequency tables for the answers (Supplementary tables S3–S6).

Logistic regression was used to evaluate whether low social support and low decision latitude at work were associated with RA risk, first in a model controlling only for the matching variables. Given that only the first part of EIRA included questions on decision latitude, we show baseline characteristics and the unadjusted analyses for those individuals separately since the fully adjusted model was limited to that group.

Subsequently, the association between these two exposures and risk of RA was evaluated in a multivariate model, adjusted also for smoking, obesity, and university degree (Table 1).

Next, we investigated whether the pattern of other modifiable factors was similar among exposed compared to non-exposed individuals, separately for cases and controls.

Statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA). All tests were two sided and the significance level was set to 0.05.

Ethics

The study was approved by the Ethical Review Board at Karolinska Institutet, Stockholm, Sweden (reference number 2015/1834-31/2). All participants in the study gave their written informed consent.

Results

Characteristics of the RA cases and matched controls are shown in Table 1. We confirmed the following risk factors for RA: no university degree [odds ratio (OR) 1.50, 95% confidence interval (CI) = 1.37–1.67], obesity (OR 1.15, 95% CI = 1.02–1.30), and current cigarette smoking (OR 1.71, 95% CI = 1.55–1.89).

Associations between low social support, low decision latitude, and risk of RA

There were 898 cases and 1381 controls reporting low social support (Table 2). Low social support was not associated with risk of RA, neither when adjusted only for matching variables (OR = 1.05, 95% CI = 0.95–1.15) nor after further adjustment for smoking, obesity, and university degree (OR = 1.00, 95% CI = 0.91–1.11). When we performed a sensitivity analysis comparing each quartile to the highest quartile, this only changed the result marginally (Supplementary table S7).

There were 285 cases and 306 controls reporting low decision latitude at work. Low decision latitude at work was associated with risk of RA in the analysis adjusted for

Table 1. Risk of rheumatoid arthritis associated with demographic, lifestyle, and occupational characteristics of participants in the EIRA study, 1996–2015, and distribution of these factors in the whole study population as well as in part 1 only (1996–2006).*

	All (N = 9660)	In multivariate model (N = 2827)	Unadjusted OR (95% CI)†	Unadjusted OR (95% CI) for patients in multivariate model	Adjusted OR (95% CI)§
Age (years)	52.3 ± 13.1	48.4 ± 10.9	‡	‡	‡
Male gender	2732 (28.3)	852 (30.1)	‡	‡	‡
Smoking	1966 (20.4)	660 (23.4)	1.71 (1.55–1.89)	1.45 (1.22–1.73)	1.71 (1.28–2.30)
BMI > 30 kg/m^2	1275 (13.2)	324 (11.5)	1.15 (1.02–1.30)	0.98 (0.78–1.24)	1.04 (0.70–1.55)
No university degree	6881 (71.3)	1989 (70.4)	1.50 (1.37–1.67)	1.32 (1.20–1.56)	1.38 (1.02–1.87)
Physical inactivity‖	327(7.7)	216 (7.7)	0.98 (0.78–1.23)	0.90 (0.68–1.20)	1.05 (0.84–1.32)
Low social support	2279 (23.8)	595 (20.8)	1.05 (0.95–1.15)	1.02 (0.85–1.23)	1.00 (0.91–1.11)
Low decision latitude¶	591 (6.1)	590 (20.5)	1.52 (1.20–1.94)	1.61 (1.25–2.07)	1.24 (0.93–1.63)

Data are shown as n (%) or mean ± sd.
*Data on occupational conditions (decision latitude) were only collected in part 1; thus, the full multivariate model is only based on part 1.
†Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated using logistic regression. Cases and controls were matched for age, gender, and residential area, so all analyses were adjusted for these parameters, and therefore it was not applicable to calculate the risk of these variables (‡).
§Further adjustment for current smoking, no university degree, obesity, and low decision latitude, when appropriate.
‖Information about physical activity was only available in EIRA 1 (cases: N = 1998; controls: N = 2252), which was run 1996–2006, since the questionnaire was modified in EIRA 2 (years 2007–2015).
¶Information about occupational conditions was only available in EIRA 1 (cases: N = 1998; controls: N = 2252). Only study participants working at the time of inclusion were eligible (N = 2827); missing data were due to retirement, studies, disability pension, etc.
Numbers of individuals with missing data are as follows: body mass index (BMI) n = 33, university degree n = 8, physical inactivity n = 5418, social support n = 73, low decision latitude n = 6833. Missing data in the model with information on occupational conditions: physical inactivity n = 4, social support n = 8.

Table 2. Characteristics of incident rheumatoid arthritis (RA) cases and controls matched for age, gender, and residential area included in the EIRA study parts 1 and 2, 1996–2015, stratified for their perceived social support.*

	Low social support	Not low social support	OR (95% CI)†	p
RA cases	(N = 898)	(N = 2802)		
Age at inclusion (years)	53.9 ± 12.1	51.7 ± 13.2	1.01 (1.01–1.02)	< 0.0001
Male gender	321 (35.7)	722 (25.8)	1.60 (1.40–1.83)	< 0.0001
ACPA positive	581 (64.7)	1818 (64.9)	0.86 (0.27–2.74)	0.80
RF positive	590 (65.7)	1842 (65.7)	1.01 (0.86–1.18)	0.95
Current smoking	281 (31.3)	679 (24.2)	1.46 (1.26–1.70)	< 0.0001
Obesity (BMI > 30 kg/m^2)	152 (16.9)	374 (13.4)	1.29 (1.09–1.54)	0.004
No university degree	766 (85.3)	2053 (73.3)	2.04 (1.77–2.36)	< 0.0001
Physical inactivity‡	67 (14.2)	85 (5.6)	2.78 (1.98–3.90)	< 0.0001
Controls	(N = 1381)	(N = 4505)		
Age at inclusion (years)	54.1 ± 12.2	51.8 ± 13.4	1.01 (1.01–1.02)	< 0.0001
Male gender	514 (37.2)	1155 (25.6)	1.60 (1.37–1.88)	< 0.0001
Current smoking	294 (21.3)	704 (15.6)	1.42 (1.21–1.68)	< 0.0001
Obesity (BMI > 30 kg/m^2)	204 (14.8)	534 (11.9)	1.33 (1.08–1.63)	0.007
No university degree	1088 (78.8)	2911 (64.6)	2.11 (1.73–2.59)	< 0.0001
Physical inactivity‡	74 (13.9)	101 (5.9)	2.57 (1.87–3.53)	< 0.0001

Data are shown as mean ± sd or n (%).
*Findings on cases and controls are presented separately to explore potential disease-specific patterns.
†Logistic regression analysis, comparing within cases and subsequently within the control group those reporting low social support vs not.
‡Only from EIRA 1 since the questionnaire on physical activity was modified in EIRA 2 (cases: N = 1991, low = 473, not low = 1518; controls: N = 2238, low = 532, not low = 1706).
ACPA, anti-citrullinated protein antibody; RF, rheumatoid factor; BMI, body mass index; OR, odds ratio; CI, confidence interval.

matching variables only (OR = 1.52, 95% CI = 1.20–1.94), but this association was weakened and statistical significance was lost after adjustments for current smoking habits, educational level, and obesity (OR = 1.28, 95% CI = 0.96–1.71).

Association between social support, decision latitude at work, and other modifiable risk factors

Among cases, those reporting low social support were more often male (OR 1.60, 95% CI = 1.40–1.83), current cigarette

Table 3. Characteristics of incident rheumatoid arthritis (RA) cases and controls matched for age, gender, and residential area included in the EIRA study, 1996–2006, when questions about control at work were included, stratified for their perceived decision latitude.*

	Low decision latitude	High decision latitude	OR (95% CI)†	p
RA cases	(N = 285)	(N = 189)		
Age at inclusion (years)	47.4 ± 11.7	48.3 ± 10.4	1.01 (0.99–1.02)	0.36
Male gender	55 (19.3)	71 (37.6)	0.40 (0.26–0.60)	< 0.0001
ACPA positive	181 (64.2)	129 (69.7)	1.29 (0.86–1.91)	0.22
RF positive	189 (66.3)	127 (67.2)	1.04 (0.70–1.54)	0.84
Current smoking	97 (34.0)	38 (20.1)	2.05 (1.33–3.16)	0.001
Obesity (BMI > 30 kg/m^2)	29 (10.2)	22 (11.6)	0.86 (0.48–1.55)	0.61
No university degree	255 (89.5)	96 (50.8)	8.23 (5.13–13.22)	< 0.0001
Physical inactivity	28 (9.8)	9 (4.8)	2.17 (1.00–4.73)	0.048
Controls	(N = 306)	(N = 309)		
Age at inclusion (years)	47.1 ± 12.1	47.5 ± 10.9	1.00 (0.99–1.02)	0.66
Male gender	68 (22.2)	109 (35.3)	0.52 (0.37–0.75)	0.0004
Current smoking	68 (22.2)	40 (12.9)	1.92 (1.25–2.95)	0.003
Obesity (BMI > 30 kg/m^2)	38 (12.4)	24 (7.8)	1.68 (0.98–2.88)	0.056
No university degree	271 (88.6)	118 (38.2)	12.53 (8.21–19.07)	< 0.0001
Physical inactivity	27 (8.8)	23 (7.4)	1.2 (0.67.2.15)	0.53

Data are shown as mean ± sd or n (%).
*Findings on cases and controls are presented separately to explore potential disease-specific patterns.
†Logistic regression analysis comparing within cases and subsequently within the control group those reporting low decision latitude at work vs high decision latitude at work.
ACPA, anti-citrullinated protein antibody; RF, rheumatoid factor; BMI, body mass index; OR, odds ratio; CI, confidence interval.

smokers (OR 1.46, 95% CI = 1.26–1.70), obese (OR 1.29, 95% CI = 1.09–1.54), with no university degree (OR 2.04, 95% CI = 1.77–2.36), and physically inactive (OR 2.98, 95% CI = 1.98–3.90). The distribution of modifiable risk factors was similar in cases and controls (Table 2).

Among RA cases, those reporting low decision latitude at work were more often current smokers (OR 2.05, 95% CI = 1.33–3.16) and had no university degree (OR 8.23, 95% CI = 5.13–13.22). Further, those with low decision latitude were more often female (OR = 2.52, 95% CI = 1.66–3.81), while the frequency of obesity did not differ (OR 0.86, 95% CI = 0.48–1.55) and differences in physical inactivity were borderline significant compared to cases not reporting low decision latitude at work (OR 2.17, 95% CI = 1.00–4.73). The pattern was similar in the control population (Table 3).

Discussion

In this large population-based study on incident RA, we found that low decision latitude at work was associated with risk of RA, but that this association was weakened after adjustment for other modifiable risk factors. Concerning levels of social support, we did not find any association between low levels of support and risk of RA, even before adjustment for known risk factors.

A report from a Dutch cohort investigated the relationship between social support and the risk of seropositive arthralgia – a condition that often precedes RA and found no association between low social support and RA risk in this group (15).

The main strength of the present study is the population-based design, with high response rates, minimizing selection bias. Another strength is the study size, along with detailed data on environmental and lifestyle factors, which enabled subgroup analyses, to better understand the relationships between those exposures and known risk factors. The recruitment of incident cases lowers the risk of bias due to reverse causation, although cohort design would be needed to capture the exposures before symptom onset among cases. However, since we did not find an association between social stressors and RA risk, this eventual bias has not yielded false-positive findings in this case. Furthermore, this study was performed within the Swedish welfare system, with general access to healthcare. A possible limitation of our study is that we cannot rule out that our results are, to some extent, affected by recall bias. Furthermore, potential non-differential misclassification of the main exposures may have contributed to biasing the studied associations towards the null value.

It is not possible from epidemiological investigations to definitely determine which of these associated factors may be causally related to disease development; such investigation would rely on more mechanistic studies, such as those performed on smoking and RA (1).

Conclusion

In the clinical setting, there is an increasing focus on primary disease prevention and individualized care, including modification of lifestyle factors associated with the risk of RA.

Our findings of a coexistence between low decision latitude at work and known modifiable environmental

and socioeconomic risk factors for RA demonstrate that a population at increased risk of RA is characterized by multiple risk factors that have to be viewed in context when considering supportive actions to diminish RA risk. Low social support falls into the same category as low decision latitude at work in also being associated with known environmental and socioeconomic risk factors, despite lacking an independent association with RA even before adjustment for known RA risk factors.

Availability of data and materials

The data sets used and/or analysed during the current study are available from the corresponding author on request. The authors declare no competing interests.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Supporting information

Additional Supporting Information may be found in the online version of this article.

Supplementary figure S1. Flowchart for number of cases with data on social support.
Supplementary figure S2. Flowchart for number of cases with data on decision latitude.
Supplementary table S1. Description of the questions on social support with frequency tables over the distribution of answers in controls and cases.
Supplementary table S2. Description of the questions on decision latitude at work with frequency tables over the distribution of answers in controls and cases who were working at the time of inclusion.
Supplementary table S3. Distribution of answers to questions on social support among controls.
Supplementary table S4. Distribution of answers to questions on social support among cases.
Supplementary table S5. Distribution of answers to questions on decision latitude among controls.
Supplementary table S6. Distribution of answers to questions on decision latitude among cases.
Supplementary table S7. Additional analysis to explore the risk associated with other than lowest quartile of answers to questions on the main exposures, social support and decision latitude, separately compared to the highest quartile.

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