Study protocol for analyses of the association between psychosocial work environment exposures and risk of autoimmune rheumatic diseases. A study protocol from the EU-funded EXIMIOUS project

Nielsen, Helena Breth; Sejbæk, Camilla Sandal; Dreyer, Lene Wohlfahrt; Madsen, Ida E. H. ; Meulengracht Flachs, Esben; Hougaard, Karin Sørig

DOI (link to publication from Publisher):
10.6084/m9.figshare.24745563.v1.

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Study protocol for analyses of the association between psychosocial work environment exposures and risk of autoimmune rheumatic diseases. A study protocol from the EU-funded EXIMIOUS project.

Authors: Helena Breth Nielsen, PhD[1], Camilla Sandal Sejbæk, PhD[2], Lene Wohlfahrt Dreyer, PhD[3], Ida E. H. Madsen, PhD[1, 4], Esben Meulengracht Flachs, PhD[2], Karin Sørig Hougaard, PhD[1, 5]

Author affiliation

[1] The National Research Centre for the Working Environment, Copenhagen, Denmark

[2] Department of Occupational and Environmental Medicine, Copenhagen University Hospital – Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark

[3] Center for Rheumatic Research Aalborg, Department of Rheumatology, Aalborg University Hospital, Aalborg University, Aalborg, Denmark.

[4] National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

[5] Department of Public Health, University of Copenhagen, Copenhagen, Denmark

Date: December 15th, 2023

Tentative title of paper: Occupational history of psychosocial work environment exposures and risk of autoimmune rheumatic diseases - A Danish register-based cohort study.

Aim: To study the association between psychosocial work environment exposures and risk rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus.

Design: A register-based cohort study.

Population

The study population will include all employees from the Danish Occupational Cohort (DOC*X), born in 1960 and onwards, i.e. participants born in 1960 would turn 19 years old in 1979. This was chosen to ensure a full work history and reduce the risk of prior unregistered autoimmune rheumatic disease because it allowed a two-year wash out period of prevalent cases since the Danish National Patient Register (DNPR) was initiated in 1977. Only employees with at least one valid occupational code (ISCO88) between 1979 and 2018 were included. We excluded employees who died, emigrated or were diagnosed with *Rheumatoid Arthritis* (RA) (ICD-8: 71219, 71229, 71238, 71239, 71259 and ICD-10: M05, M050, M051, M051A-F, M052, M053, M058, M059, M06, M060, M062, M064 , M068, M069), *Systemic Sclerosis* (SS) (IDC-8: 73400, 73401, 73402, 73408, 73409, 73491 and ICD-10: M34, M340, M341, M342, M342A, M342B, M348, M348B, M349) and *Systemic Lupus Erythematosus* (SLE) (ICD-8: 73419 and ICD-10: M32, M320, M321, M328, M329) or Juvenile Idiopathic Arthritis (ICD-8: 71209 and ICD-10: M08) before age 19 years.

Exposures – psychosocial work environment exposures

We used Job Exposure Matrices (JEM) on psychosocial work exposures developed by Madsen et al. 2018 (1) and Framke et al. 2021 (2). For each exposure, a sex- and age-specific JEM has been constructed based on self-reported survey information. We will use the estimated exposure levels assigned to occupations coded according to Statistics Denmark's Standard Classification of Occupations (DISCO-88), a Danish version of the International Standard Classification of Occupations (ISCO-88). JEM estimates for Quantitative demands, Decision authority, Emotional demands, Job insecurity and Physical violence are based on survey information from the *Work Environment and Health in Denmark* survey in 2012 (1). In these JEMs, the continuous exposures (Quantitative demands, Decision authority and Emotional demands) were modelled by the predicted mean level using best linear unbiased prediction (BLUP) from a generalized linear mixed model with a random intercept for the job group (1). Job insecurity and Physical violence were estimated as the predicted probabilities of exposure given job group, sex and age. Role conflicts at work and Possibilities for development at work were based on survey information from the *Danish Work Environment Cohort Study* in 2000 and 2005 (2). The JEM on Possibilities for development at work were estimated as the mean values from multilevel modelling, while Role conflict were dichotomized and modelled as the predicted probability given job group, sex, age and year of data collection (2).

The following exposures were included:

1. ***Quantitative demands***
   Quantitative demands were defined as the mean score of the five items: 1) "Do you have time enough for your work tasks?", 2) "Do you have deadlines that are difficult to keep?", 3) "Do you get unexpected work tasks that put you under time pressure?", 4) "Are you available outside normal working hours?" and 5) "Do you have to work overtime?", which was each scored from 1 (never) to 5 (always).

2. ***Decision authority***
   Decision authority was defined as the mean score of the two items: 1) "Can you influence how you solve your work tasks?" and 2) "Can you influence when you solve your work tasks?", which was each scored from 1 (never) to 5 (always).

3. ***Emotional demands***
   Emotional demands were assessed as the mean score of the two items: 1) "Do you get emotionally involved in your work?" 2) "Do you have to deal with the problems of e.g. clients, patients or students in your work (not problems of your colleagues)?", each scored from 1 to 5 (higher emotional demands).

4. ***Job insecurity***
   Job insecurity was assessed by the item: "Are you worried about becoming unemployed?" that was dichotomized into high ("to a very high extent" or "to a high extent") and low ("to some extent", "to a low extent" or "to a very low extent").

5. ***Physical violence***
   Physical violence is a probability-based exposure assessed by the item: "Have you within the past 12 months been exposed to physical violence at your workplace?" with the responses "yes" or "no".

6. ***Role conflicts at work***
   Role conflicts at work were assessed by one self-reported item: "Are contradictory demands placed on you at work?", dichotomized into Yes ("yes, certainly") and No ("no, not at all" or "from time to time").

7. ***Possibilities for development at work***
   Possibilities for development at work were assessed by the mean score of the three items: 1): "Does your work require you to take the initiative?", 2) "Do you have the possibility of learning new things through your work?" and 3) "Can you use your skills or expertise in your work?", each scored from 1 to 5 (higher levels of possibility for development).

Finally, we will include a **psychosocial index** which will sum the number of adverse psychosocial work environment exposures for each person per year. Adverse psychosocial work environment exposures will be evaluated as: the top quartile of the annual quartile levels of exposure in the population for Quantitative job demands, Emotional demands, Role conflict, Job insecurity and Physical violence; and lowest quartile in Decision authority and Possibilities for development at work.

For each exposure, we will use the age- and sex-specific JEM estimates for each job group. If no JEM estimate were available at the four-level job code, we will use the three-level job code, then the two-level job code and as a last choice we will use only the first digit in the job code. For the JEMs (Quantitative demands, Decision authority, Emotional demands, Job insecurity and Physical violence), which were based on data from only one time point (2012), the exposure estimates will be assumed to be constant within each job group across calendar years. For the JEMS (Role conflict and Possibilities for development), with exposure estimates on two time points (2000 and 2005), we will assign the 2000 estimates to 1979-2000 and the 2005 estimates to 2001-2018. Thus, the sex and age specific values from the JEMs will be extrapolated to previous and future calendar years.

When participants are gainfully employed (employed or self-employed or assisting spouse) but have a missing job code, we will extrapolate the occupational codes (DISCO88 code) of that person's previous job (and corresponding JEM estimate) by using the most recent occupational code up to five years back in time, in line with (3). Yet, if no job codes were available after extrapolation or no JEM estimates were available, and the person was registered with employment (employed or self-employed or assisting spouse), we assigned the exposure estimate for a missing job code.

Each exposure measure will be evaluated as time-varying and continuous for each person:

- **Recent exposure**: Exposure level within the previous year divided into annual population quartiles.
- **Accumulated exposure**: Sum of exposure across work life, i.e. since entrance to the labour market and until recent exposure (included). Since Physical violence, Job insecurity and Role conflict are probabilities, we will not be calculating an accumulated measure for these.
- **High exposure years**: Number of years across work-life with high exposure level, since entrance to the labour market and until the recent exposure (included). A high exposure level will be assessed as the top quartile of the annual quartile levels of exposure in the population, except for Decision authority and Possibilities for development at work, where we will use the lowest quartile.

Exposure information will be lagged one year from the outcome, i.e. the exposure (at t-1) is measured the year prior to the outcome and other independent variables (at t0). In case an employee is not employed (defined as not employed, self-employed or assisting spouse) at t-1 the JEM estimate at t-1 will be missing. When linked to the outcome the following year (t0), the recent exposure level will be set to missing, while the accumulated exposure and high exposure years will retain the exposure level assigned to the year before the missing value (at t-2)

Outcome - Autoimmune rheumatic diseases

We included the following autoimmune rheumatic diseases: *Rheumatoid Arthritis (RA), Systemic Sclerosis (SS)* and *Systemic Lupus Erythematosus (SLE)*. We will identify cases from the DNPR and include both in – (available since 1977) and outpatient (available since 1995) contacts (4). Ibfelt et al (2017) showed a positive predictive value (PPV) of 79%, when using incident RA diagnoses recorded ≥2 times within 90 days in rheumatology departments during 2011 (5). In terms of SLE, a study found a PPV of 73% (fulfilling clinical criteria) when using a definition of one SLE registration in the DNPR. Yet, when a second criteria was applied of: 1) followed by either 1 year of out-patient follow-up, or 2) inpatient admissions due to SLE

diagnosis within less than 3-months during the first year of follow-up, the PPV increased to 89% (6). Thus, to reduce the risk of misclassification due to false-positive cases, we did not include the cases untill their second AID registration.

The following ICD-8 and ICD-10 codes will be included:

Rheumatoid arthritis (RA)

- ICD-8: 71219, 71229, 71238, 71239, 71259
- ICD-10: M05, M050, M051, M051A-F, M052, M053, M058, M059, M06, M060, M062, M064, M068, M069
    - Incl. previous ICD-10 codes: M053A-E (now: M053) and DM050A (now: M050) (7).

Systemic sclerosis (SS)

- ICD-8: 73400, 73401, 73402, 73408, 73409
- ICD-10: M34, M340, M341, M342, M342A, M342B, M348, M348B, M349
    - Incl. previous ICD-10 codes: DM348C (now: DM348) (7).

Systemic lupus erythematosus (SLE)

- ICD-8: 73419
- ICD-10: M32, M321, M328, M329
    - Incl. previous ICD-10 codes: M321A-E (now: M321) (7).

Covariates

Based on previous literature on autoimmune rheumatic diseases (8-15), we constructed a directed acyclic graph (DAG, see appendix). As a result, the following models were constructed to adjust for confounding (see appendix for list of variables and coding):

Minimal adjusted model:

- Exposure at interest. Time-dependent and measured annually. The recent exposure will be included as a categorical variable. The accumulated exposure and number of high exposure years will be included as continuous variables.
- Age. Time-dependent and measured annually. Age will be included as a continuous variable with a quadratic term.
- Sex (women/men). Time independent, at baseline. Sex will be included as a categorical variable.

Model 1 (main model):

- Minimal adjusted model
- Calendar year (categorized by 5-year intervals). Time-dependent, measured yearly. Calendar year will be included as a categorical variable.

- Highest attained education (Primary or lower secondary, Upper secondary, Short cycle tertiary, Bachelor or equivalent, Master or equivalent, Doctoral or equivalent, Unknown). Time-dependent, measured annually. Highest attained education will be included as a categorical variable.
- Ethnicity (Danish, immigrants or descendants). Time fixed at baseline. Ethnicity will be included as a categorical variable.

Model 2 (possible over-adjusted model):

- Model 1
- Years of non-employment (calculated as the number of years without an employment status of 1) employed (salaried) or 2) self-employed or assisting spouse). Time-dependent, measured annually. Years of non-employment will be included as a continuous variable.
- Family income level (divided into annual population quartiles). Time-dependent, measured annually. Family income level will be included as a categorical variable.
- Smoking (probability of active smoking). JEM-based value (16). Time-dependent, measured annually. Smoking will be included as a continuous variable.
- Obesity (mean BMI estimate). JEM-based value (16). Time-dependent, measured annually. Obesity will be included as a continuous variable.

If there are several registrations in the same year for a covariate, we will use the first registration that year.

Lag time

As the exposures are resolved annually, we included a lag time of one year from measures of exposure (t-1) to the outcome measure (t0), in line with Boudigaard et al. (2021)(3). Thus, the exposure will be measured the calendar year before the outcome. This ensures a longitudinal design and allows for some time from the first signs of symptoms to diagnosis.

Follow-up

To exclude prior cases of autoimmune rheumatic diseases, follow-up will start in 1997. This allows us to identify previous cases of in-patients from DNPR (available since 1977 in DNPR) plus a two-year washout period for prevalent cases identified from out-patients, which became available in 1995 in DNPR. The study population will be followed between January 1st, 1997 and December 31st, 2018. Participants will be followed from first registered job and until the first of the following events occur: clinical end-point, migration, death, or end of follow-up (December 31st, 2018).

Statistical analysis

We will analyze the associations between the psychosocial work environment exposures and autoimmune rheumatic diseases using time-to event by multilevel Poisson regression analyses, to account for clustering on main job-groups assessed by the first digit of the DISCO88 codes. The time unit is 1-year periods and the logarithm of person-years at risk will be used as an offset.

Results from the three models (minimally adjusted model, model 1 and model 2) will be presented with incidence rate ratio (IRR) estimates and 95% Confidence Intervals (CI). We will present results for the combined outcome (with RA, SS and SLE) and separate tables for each disease, i.e. one for RA, SS and SLE. In the combined analysis, if an individual had several diagnoses of autoimmune rheumatic diseases, the first registration as case will be used.

Analyses will be initiated after publication of this study protocol.

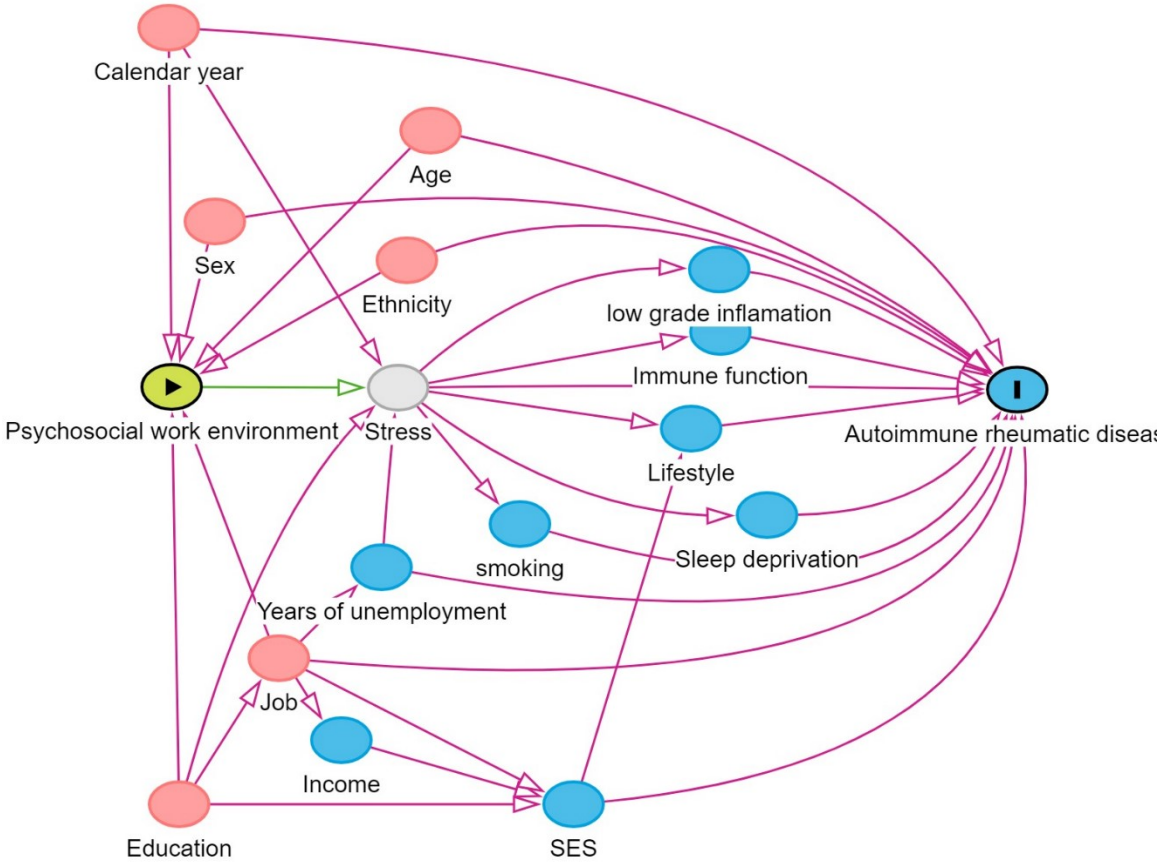
Funding

This work has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 874707 "EXIMIOUS". More information on the EXIMIOUS project can be found in Ronsmans et al. (2022) (17).

APPENDIX

Appendix - Directed Acyclic Graph (DAG)

Simplified DAG: Minimal sufficient adjustment sets for estimating the total effect of High job demands, Low job control on Rheumatoid arthritis: Age, Sex, Job, Calendar year, Education, Ethnicity.



The DAG is constructed based on literature from systematic reviews and meta-analyses. In the table below the reviews are presented by disease and exposures assessed. The quality of the evidence for the associations is presented by colours according to the included systematic reviews' evaluation of the quality of evidence: Strong, moderate, low

	Sex	Age	SES	Genetics	Ethnicity	smoking	BMI	alcohol	Urban/rural (Air pollution)	other
RA	(13)	(13)	(13)	(13)	(13)	(11) (13)	(14) (13)			silica(15), diet (13)
SS	(9) More F	(9) peak 45-64 years old		(9)	(9)	NOT (9)		NOT (9)		Silica (9), low vitamin D (9), NOT infections(9), heavy metals(9), low birth weight(9), organic solvents(9),
LU	(8) More F	(8) M later onset	(8)	(8)	(8)	(8, 12)	(8)	Inverse in F (8)	(8)	Endomitriose (8), silica (8), low vitamin D (8), infections (8), pesticides (8), diet (8)

Appendix – List of variables and coding

Variable	Type	Categories	Register	Original codes
Age	Time dependent Continuous	For descriptive table: 18-24 years old 25-34 years old 45-58 years old	DOC*X (Foed_dato)	Age at the end of the year (the 31th of December) round down to nearest whole number.
Sex	Time independent Categorical	Men Women	DOC*X (koen)	1 Men 2 Women
Calendar year	Time dependent Categorical	1979-1984 1984-1988 1989-1993 1994-1998 1990-1998 1999-2003 2004-2008 2009-2013 2014-2018	DOC*X, constructed	
Highest attained education	Time dependent Categorical	Primary or lower secondary Upper secondary Short cycle tertiary Bachelor or equivalent Master or equivalent Doctoral or equivalent Unknown	UDDA (hfaudd)	
Ethnicity	Time independent Categorical	Danish origin Immigrant	BEF (IE_type)	1 Danish 2 immigrant 3 Descendants 9 undisclosed
Years of non-employment	Time dependent Continuous	Years without employment Years with employment	DOC*X, constructed (besk_status)	3 Unemployed . Missing 1 Employed (salaried) 2 Self-employed or assisting spouse
Family income level	Time dependent Categorical	Annual quartiles	FAIK (familie_indkomst)	
Smoking	Time dependent Continuous	Estimated percentage of active smokers	JEM (smoke_p_jem_level_1-4)	
Obesity	Time dependent Continuous	Estimated mean BMI	JEM (bmi_jem_level_1-4)	

References

1. Madsen IEH, Gupta N, Budtz-Jorgensen E, Bonde JP, Framke E, Flachs EM, et al. Physical work demands and psychosocial working conditions as predictors of musculoskeletal pain: a cohort study comparing self-reported and job exposure matrix measurements. Occup Environ Med. 2018;75(10):752-8.

2. Framke E, Sorensen JK, Alexanderson K, Farrants K, Kivimaki M, Nyberg ST, et al. Emotional demands at work and risk of long-term sickness absence in 1.5 million employees in Denmark: a prospective cohort study on effect modifiers. Lancet Public Health. 2021;6(10):E752-E9.

3. Boudigaard SH, Schlunssen V, Vestergaard JM, Sondergaard K, Toren K, Peters S, et al. Occupational exposure to respirable crystalline silica and risk of autoimmune rheumatic diseases: a nationwide cohort study. Int J Epidemiol. 2021;50(4):1213-26.

4. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-89.

5. Ibfelt EH, Sorensen J, Jensen DV, Dreyer L, Schiottz-Christensen B, Thygesen PH, et al. Validity and completeness of rheumatoid arthritis diagnoses in the nationwide DANBIO clinical register and the Danish National Patient Registry. Clin Epidemiol. 2017;9:627-32.

6. Hermansen ML, Lindhardsen J, Torp-Pedersen C, Faurschou M, Jacobsen S. Incidence of Systemic Lupus Erythematosus and Lupus Nephritis in Denmark: A Nationwide Cohort Study. J Rheumatol. 2016;43(7):1335-9.

7. Health NBo. Hjælpelister til ny udgave af "Klassifikation af sygdomme" pr. 1. januar 2012 (22. dec. 2011) [Help lists for the new edition of "Classification of diseases" per January 1, 2012 (December 22, 2011)] 2011 [Available from: https://sundhedsdatastyrelsen.dk/-/media/sds/filer/rammer-og-retningslinjer/klassifikationer/kodeaendringer/koder-der-erstattes-af-nye-koder-pdf.pdf?la=da.

8. Gergianaki I, Bortoluzzi A, Bertsias G. Update on the epidemiology, risk factors, and disease outcomes of systemic lupus erythematosus. Best practice & research Clinical rheumatology. 2018;32(2):188-205.

9. Abbot S, Bossingham D, Proudman S, de Costa C, Ho-Huynh A. Risk factors for the development of systemic sclerosis: a systematic review of the literature. Rheumatology advances in practice. 2018;2(2):rky041.

10. Ohno T, Aune D, Heath AK. Adiposity and the risk of rheumatoid arthritis: a systematic review and meta-analysis of cohort studies. Scientific reports. 2020;10(1):16006.

11. Di Giuseppe D, Discacciati A, Orsini N, Wolk A. Cigarette smoking and risk of rheumatoid arthritis: a dose-response meta-analysis. Arthritis research & therapy. 2014;16(2):R61.

12. Jiang F, Li S, Jia C. Smoking and the risk of systemic lupus erythematosus: an updated systematic review and cumulative meta-analysis. Clinical rheumatology. 2015;34(11):1885-92.

13. Arleevskaya M, Takha E, Petrov S, Kazarian G, Renaudineau Y, Brooks W, et al. Interplay of Environmental, Individual and Genetic Factors in Rheumatoid Arthritis Provocation. International journal of molecular sciences. 2022;23(15).

14. Feng X, Xu X, Shi Y, Liu X, Liu H, Hou H, et al. Body Mass Index and the Risk of Rheumatoid Arthritis: An Updated Dose-Response Meta-Analysis. BioMed research international. 2019;2019:3579081.

15. Morotti A, Sollaku I, Franceschini F, Cavazzana I, Fredi M, Sala E, et al. Systematic Review and Meta-analysis on the Association of Occupational Exposure to Free Crystalline Silica and Rheumatoid Arthritis. Clin Rev Allergy Immunol. 2022;62(2):333-45.

16. Petersen SB, Flachs EM, Prescott EIB, Tjonneland A, Osler M, Andersen I, et al. Job-exposure matrices addressing lifestyle to be applied in register-based occupational health studies. Occup Environ Med. 2018;75(12):890-7.

17. Ronsmans S, Sorig Hougaard K, Nawrot TS, Plusquin M, Huaux F, Jesus Cruz M, et al. The EXIMIOUS project-Mapping exposure-induced immune effects: connecting the exposome and the immunome. Environ Epidemiol. 2022;6(1):e193.