



## ORIGINAL RESEARCH

## Effects of alcohol consumption and smoking on risk for RA: results from a Swedish prospective cohort study

Louise Hedenstierna <sup>1,2</sup>, Rino Bellocco,<sup>3,4</sup> Weimin Ye,<sup>3</sup> Hans-Olov Adami,<sup>3,5</sup> Torbjörn Åkerstedt,<sup>6,7</sup> Ylva Trolle Lagerros,<sup>8,9</sup> Anna Karin Hedström <sup>6</sup>

**To cite:** Hedenstierna L, Bellocco R, Ye W, *et al.* Effects of alcohol consumption and smoking on risk for RA: results from a Swedish prospective cohort study. *RMD Open* 2021;**7**:e001379. doi:10.1136/rmdopen-2020-001379

Received 27 June 2020

Revised 22 October 2020

Accepted 10 December 2020

## ABSTRACT

**Objective** Several, but not all studies, have shown a dose-dependent inverse association with alcohol consumption and rheumatoid arthritis (RA), whereas smoking is an established risk factor for RA. We aimed to study the association between alcohol consumption and RA incidence and investigate a potential interaction between alcohol and smoking habits, regarding RA incidence.

**Methods** We used a prospective cohort study, based on 41 068 participants with detailed assessment of alcohol intake, smoking and potential confounders at baseline in 1997. We ascertained a total of 577 incident cases of RA during a mean of 17.7 years of follow-up through linkage to nationwide and essentially complete databases. Multivariate Cox proportional hazards models were used to estimate HR with 95% CI. Interaction on the additive scale between alcohol and smoking was estimated by calculating the attributable proportion due to interaction (AP).

**Results** Overall, alcohol consumption was associated with a 30% reduced incidence of RA (HR 0.69, 95% CI 0.55 to 0.86) with a dose–response relationship (p value for trend <0.001) which remained significant after stratification by age and smoking habits. The positive association between smoking and RA incidence was reduced with increasing alcohol consumption (p value for trend <0.001). A synergistic effect was observed between alcohol and smoking (AP 0.40, 95% CI 0.15 to 0.64), indicating that 40% of the cases among the double exposed are due to the interaction per se.

**Conclusions** Our findings suggest an inverse association between alcohol consumption and RA incidence, and a synergistic effect between alcohol and smoking.

## INTRODUCTION

Rheumatoid arthritis (RA), a chronic inflammatory disease characterised by progressive joint damage and sometimes multisystem involvement, develops through interplay between genetic loci and environmental factors.<sup>1</sup> Alcohol consumption dose-dependently affects both innate and adaptive aspects of the immune system.<sup>2,3</sup> However, the impact of alcohol consumption on RA risk remains poorly understood. Several

## Key messages

## What is already known about this subject?

- ▶ Previous studies indicate that moderate intake of alcohol is protective against developing rheumatoid arthritis (RA).

## What does this study add?

- ▶ In a large prospective cohort study, we replicate findings of an inverse association between alcohol consumption and RA risk following extensive adjustment for confounders.
- ▶ In addition, we show a synergistic effect between alcohol drinking and smoking with a substantial attenuation of the protective effect of alcohol among smokers.

## How might this impact on clinical practice?

- ▶ Further studies in order to increase the understanding of the underlying mechanisms behind our findings may contribute to define new ways to achieve protection against RA.

studies have indicated an inverse relationship between alcohol consumption and RA risk,<sup>4–7</sup> although results have not been consistent.<sup>8,9</sup>

Smoking, the main environmental risk factor, is estimated to account for approximately 20% of the environmental risk for RA.<sup>10</sup> Because smoking is positively correlated with alcohol intake, these two risk factors are mutual confounders in studies of RA. As a corollary, a large case-control study showed a greater alcohol-related relative risk reduction among ever smokers than among never smokers.<sup>11</sup> In a prospective cohort study, the increased risk of RA associated with smoking was reduced among alcohol consumers.<sup>12</sup>

However, there is still a paucity of prospective studies with enough statistical power to analyse effects of various amounts of alcohol intake with concurrent data on cigarette smoking and their possible interaction. Therefore, we have used a large prospective



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For numbered affiliations see end of article.

## Correspondence to

Dr Louise Hedenstierna; louise.hedenstierna@ki.se

cohort to investigate the joint effects and potential interaction between alcohol-drinking and smoking in relation to RA risk.

## METHODS

The study is based on the Swedish National March Cohort, a prospective cohort study with nearly 42 000 participants.<sup>13</sup> The study was established in September 1997 during a nationwide fundraising event for cancer research. During the event, participants were asked to fill in a 36 pages questionnaire for epidemiological research, and in total 43 863 persons volunteered. Due to the nature of the recruitment process, the number of individuals offered the questionnaire could not be assessed. The questionnaire provided information about demographics, lifestyle factors and medical information. Participants also provided their individually unique national registration number, assigned to all Swedish residents. This number enables follow-up through linkage to multiple nationwide, continuously updated registers including medical information.

Individuals with incorrect national registration number were excluded (n=11), as were those who were younger than 18 years (n=1732) or had emigrated or died (n=55) before the start of follow-up. We also excluded subjects with a diagnosis of RA at baseline, defined as ICD-code M05-M06; diagnoses were obtained from the Swedish National Patient Registers. A previous validation of the accuracy of the diagnoses in the National Patient registers indicates that 90% of the registered patients, diagnosed with RA, fulfil either the ACR 1987 or the ACR/EULAR 2010 diagnostic criteria for RA.<sup>14</sup> Subsequently, individuals with incomplete information on alcohol use or smoking habits were excluded and the final study cohort included 41 068 individuals. We used record linkages (based on the national registration numbers) to nationwide, essentially complete and continuously updated health databases to calculate person-years and ascertain incident cases of RA. Participants were followed from baseline 1 October 1997, until diagnosis of RA (defined as above), death, emigration or 31 December 2016, whichever occurred first.

Detailed information regarding alcohol consumption was obtained, which allowed quantification of the average alcohol intake in gram per week. Subjects were categorised into the following groups based on the sex-specific distribution of alcohol intake in gram per week: non-drinkers, low consumption (below or equal to the median), moderate consumption (above the median, but below or equal to the 75th percentile) and high consumption (above the 75th percentile). Low alcohol consumption was defined as <30 g/week among women and <51 g/week among men; moderate alcohol consumption as 30–65 g/week among women and 51–104 g/week among men and high alcohol consumption as >65 g/week among women and >104 g/week among men. Smoking was dichotomised into never or ever smokers.

Information on confounding variables including sex, educational level,<sup>15</sup> body mass index,<sup>16</sup> physical activity,<sup>17</sup> coffee consumption<sup>18</sup> and cardiovascular disease were obtained from the questionnaire. Education was summarised into a binary variable, based on having reached a university degree. Body mass index was calculated by dividing weight in kilograms by height in metres squared and categorised into underweight (<18.5 kg/m<sup>2</sup>), normal weight (18.5–24.99 kg/m<sup>2</sup>), overweight (25–30 kg/m<sup>2</sup>) or obese (>30 kg/m<sup>2</sup>). Estimates of physical activity were based on reported responses on weekly exercise levels ranging from none or light physical activity to vigorous physical activity and dichotomised into those active (more than 120 min/week) or inactive (120 min or less/week). Coffee consumption was categorised into 0, 1–4, 5–7 or >7 cups of coffee per day. Information regarding diagnoses of cardiovascular disease (ICD-10 codes I00-I99) at baseline was obtained from the Swedish Patient Register and dichotomised into those who had a previous cardiovascular diagnosis and those who had not.

## Statistical analysis

Differences in baseline variables across categories of alcohol consumption were assessed using one-way analysis of variance or the Kruskal-Wallis test for continuous variables and  $\chi^2$  test for categorical variables. A Cox proportional hazards model with attained age as time-scale was used to estimate HR of developing RA with 95% CI among subjects with different alcohol consumption habits at baseline, compared with non-drinkers. The analysis was stratified by age (<60 years or  $\geq$ 60 years at baseline) and smoking habits (ever or never smoking). We assessed the proportionality hazard assumption, based on the Schoenfeld residual plots and statistical tests, and found no indication of violation for any covariate. We analysed the dose–response relationship between alcohol consumption and RA incidence by using a categorical variable for the amount of alcohol consumed per week (non-drinkers, low, moderate or high alcohol consumers as defined above) in a Cox proportional hazards model.

A potential interaction between alcohol and smoking was analysed using departure of additivity of effects as criterion of interaction and quantified by calculating the attributable proportion due to interaction (AP) with 95% CI. 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. When conducting the analyses of interaction, alcohol intake was recoded as a risk factor.<sup>19</sup>

The full Cox model was adjusted for potential confounding variables including sex, educational level,<sup>15</sup> body mass index,<sup>16</sup> physical activity,<sup>17</sup> coffee consumption<sup>18</sup> and cardiovascular disease. When appropriate, adjustment was also made for smoking.

We also performed analyses to study the association between low and moderate/high intake of alcohol and RA incidence (ie, non-drinkers were excluded). Similarly,

we studied the potential interaction between low alcohol consumption and smoking with regard to RA risk, with moderate/high consumers of alcohol who did not smoke as the reference group.

The proportion of missing data in the potential confounding variables was 4.4% for body mass index, 1.7% for coffee consumption and less than 1% for educational status, physical activity and alcohol consumption. We conducted supplementary analyses after imputing missing data using the multiple imputation chained equation procedure. We also performed a sensitivity analysis in which we excluded participants who developed RA within 5 years after baseline, when preclinical health could influence lifestyle habits. In another sensitivity analysis, we excluded current smokers.

A larger dataset than ours would be needed in order to perform the analyses stratified by gender. The majority of the cases were women, which was expected since RA is more common among women. However, when the analyses were restricted to women the results remained similar. All analyses were performed using Statistical Analysis System (SAS) 9.4.

## RESULTS

Our analyses on alcohol consumption and RA incidence included 41 068 participants. Characteristics of participants at baseline, overall and by alcohol consumption habits, are presented in [table 1](#). Generally, alcohol consumers were younger and had a higher educational level than non-drinkers. They more often reported shift work and slightly shorter habitual sleep duration. Alcohol consumption and smoking were highly correlated ( $p < 0.001$ ).

During a mean follow-up time of 17.7 years (median 18 years), 577 participants were diagnosed with RA. The

average age at the time of RA diagnosis was 66.8 years (SD 12.8).

Overall, alcohol consumption was associated with a 30% reduced incidence of RA (HR 0.69, 95% CI 0.55 to 0.86) with an inverse dose–response relationship between weekly amount of alcohol consumption and RA incidence ( $p$  value for trend  $< 0.001$ , [table 2](#)). After stratification by age ( $< 60$  years and  $\geq 60$  years at baseline), estimates remained similar in both groups ([table 3](#)). Among drinkers, 89% reported intake of more than one type of alcoholic beverage. While 9.9% reported exclusively intake of other alcoholic beverages than wine, 6.9% reported exclusively intake of wine. There was no significant difference between those who exclusively drank wine (HR 0.66, 95% CI 0.45 to 0.96) or other types of alcoholic beverages than wine (HR 0.69, 95% CI 0.56 to 0.86).

The impact of alcohol on RA incidence was more pronounced among ever smokers than among never smokers, although the inverse correlation between amount of alcohol consumption and RA incidence remained statistically significant also among never smokers ([table 3](#)). Smoking increased RA incidence with a HR of 2.80 (95% CI 1.96 to 4.01) among non-drinkers, whereas the corresponding HR was 1.45 (95% CI 1.21 to 1.74) among alcohol consumers.

With regard to RA incidence, we found a significant interaction on the additive scale between alcohol and smoking ([table 4](#)). The AP was 0.40 (95% CI 0.15 to 0.64), indicating that the combined effect was 40% higher than the sum of the individual effects or equivalently, that 40% of the cases among the double exposed are due to the interaction per se. The result remained similar when participants who had developed RA during the first 5 years after baseline were excluded (AP 0.40,

**Table 1** Baseline characteristics, overall and by alcohol consumption habits

Variable	Total	Alcohol consumption				P value
		None	Low	Moderate	High	
N	41 068	5475	17 761	9035	8797	
Mean age (SD)	51.5 (15.9)	56.4 (17.1)	52.6 (15.9)	50.2 (14.9)	47.8 (15.3)	$< 0.001$
Women, n (%)	26 613 (65)	3839 (70)	11 353 (64)	5833 (65)	5588 (64)	$< 0.001$
University degree, n (%)	11 497 (28)	1086 (20)	4401 (25)	2904 (32)	3106 (35)	$< 0.001$
Ever smokers, n (%)	16 437 (40)	1040 (19)	6566 (37)	4130 (46)	4701 (53)	$< 0.001$
BMI, kg/m <sup>2</sup> (SD)	24.6 (3.5)	24.9 (3.9)	24.7 (3.6)	24.5 (3.3)	24.4 (3.3)	$< 0.001$
Low physical activity, n (%)	6320 (15)	784 (14)	2631 (15)	1380 (15)	1525 (17)	$< 0.001$
Sleep duration, hours/night (SD)	6.8 (1.0)	6.9 (1.1)	6.8 (1.0)	6.8 (1.0)	6.8 (1.0)	$< 0.001$
Shift work, n (%)	2315 (5.6)	213 (4.2)	1065 (6.0)	518 (5.7)	501 (5.7)	$< 0.001$
Cardiovascular disease, n (%)	4539 (11)	822 (15)	2109 (12)	871 (10)	737 (8.4)	$< 0.001$

Differences in baseline variables across categories of alcohol consumption were assessed using one-way ANOVA or Kruskal-Wallis test for continuous variables and  $\chi^2$  test for categorical variables. Alcohol consumption was categorised into low consumption ( $< 30$  g/week among women and  $< 51$  g/week among men), moderate consumption (30–65 g/week among women and 51–104 g/week among men) and high consumption ( $> 65$  g/week among women and  $> 104$  g/week among men). ANOVA, analysis of variance; BMI, body mass index.

**Table 2** HR with 95% CI of developing RA among subjects with different alcohol consumption habits

Alcohol consumption	N	Person years	Incident RA (%)	HR (95% CI)*	HR (95% CI)†
None	5475	91 922	103 (1.9)	1.0 (reference)	1.0 (reference)
Low	17 761	311 888	262 (1.5)	0.82 (0.65–1.03)	<b>0.76 (0.60–0.96)</b>
Moderate	9035	162 535	117 (1.3)	<b>0.72 (0.55–0.95)</b>	<b>0.65 (0.49–0.86)</b>
High	8797	160 250	95 (1.1)	<b>0.62 (0.47–0.83)</b>	<b>0.54 (0.41–0.73)</b>
					P for trend <0.001

Significant HRs are in bold.

Low alcohol consumption (<30 g/week among women and <51 g/week among men); moderate alcohol consumption (30–65 g/week among women and 51–104 g/week among men); high alcohol consumption (>65 g/week among women and >104 g/week among men).

\*Adjusted for gender.

†Adjusted for gender, educational status, smoking, body mass index, physical activity and cardiovascular disease.

RA, rheumatoid arthritis.

95% CI 0.13 to 0.67). The interaction between smoking and alcohol also remained similar when the analysis was restricted to include past smokers (AP 0.44, 95% 0.16 to 0.72).

Overall, high alcohol consumption versus low alcohol consumption rendered an HR of 0.71 (95% CI 0.56 to 0.91). The inverse dose–response relationship between the amount of alcohol consumption and RA incidence remained significant when non-drinkers were excluded (p value for trend <0.001). An interaction was observed between low alcohol consumption and smoking with regard to RA risk (AP 0.22, 95% CI 0.02 to 0.52) (table 5). Our results remained almost identical following multiple imputed data (data not shown).

## DISCUSSION

Our results confirm an inverse dose–response relationship between alcohol consumption and RA incidence as well as a positive association with smoking. The risk reduction associated with alcohol consumption was more pronounced among smokers. In addition, alcohol acted synergistically with smoking to increase RA incidence.

When we analysed the association between alcohol and RA incidence, non-drinkers were used as the reference category in the main analyses. Because concerns have been raised regarding the possibility of uncontrolled or residual confounding when drinkers are compared with non-drinkers in observational studies,<sup>20 21</sup> we also

**Table 3** HR with 95% CI of developing RA among subjects with different alcohol consumption habits, stratified by age and smoking habits

Alcohol consumption	Age <60 years				Age ≥60 years			
	N	Person years	Incident RA (%)	HR (95% CI)*	N	Person years	Incident RA (%)	HR (95% CI)*
None	2717	49 994	51 (1.9)	1.0 (reference)	2758	41 928	52 (1.9)	1.0 (reference)
Low	11 147	207 777	149 (1.3)	<b>0.72 (0.52–0.99)</b>	6614	104 112	113 (1.7)	0.75 (0.55–1.04)
Moderate	6501	121 636	78 (1.2)	<b>0.63 (0.44–0.91)</b>	2534	40 890	39 (1.5)	<b>0.66 (0.44–0.99)</b>
High	6816	127 736	67 (1.0)	<b>0.53 (0.36–0.77)</b>	1981	32 514	28 (1.4)	<b>0.55 (0.35–0.87)</b>
					P for trend 0.01			
Alcohol consumption	Ever smokers				Never smokers			
	N	Person years	Incident RA (%)	HR (95% CI)†	N	Person years	Incident RA (%)	HR (95% CI)†
None	1040	16 920	35 (3.4)	1.0 (reference)	4435	75 002	68 (1.5)	1.0 (reference)
Low	6566	113 202	129 (2.0)	<b>0.60 (0.41–0.88)</b>	11 195	198 686	133 (1.2)	0.81 (0.60–1.09)
Moderate	4130	73 387	67 (1.6)	<b>0.49 (0.32–0.73)</b>	4905	89 149	50 (1.0)	0.71 (0.49–1.03)
High	4701	84 869	58 (1.2)	<b>0.38 (0.25–0.58)</b>	4096	75 381	37 (0.9)	<b>0.67 (0.44–0.99)</b>
					P for trend 0.001			
					P for trend 0.03			

Significant HRs are in bold.

Low alcohol consumption (<30 g/week among women and <51 g/week among men); moderate alcohol consumption (30–65 g/week among women and 51–104 g/week among men); high alcohol consumption (>65 g/week among women and >104 g/week among men).

\*Adjusted for gender, educational status, smoking, body mass index, physical activity and cardiovascular disease.

†Adjusted for gender, educational status, body mass index, physical activity and cardiovascular disease.

RA, rheumatoid arthritis.

**Table 4** HR with 95% CI of developing RA among subjects with different combinations of alcohol consumption and smoking

Alcohol consumption	Ever smoking	N	Person years	Incident RA	HR (95% CI)*	HR (95% CI)†	AP (95% CI)
Yes	No	20 196	363 215	220 (1.1)	1.0 (reference)	1.0 (reference)	
No	No	4435	75 002	68 (1.5)	1.27 (0.97–1.68)	1.25 (0.95–1.64)	
Yes	Yes	15 397	271 459	254 (1.7)	<b>1.49 (1.24–1.79)</b>	<b>1.45 (1.21–1.74)</b>	
No	Yes	1040	16 920	35 (3.4)	<b>3.03 (2.12–4.33)</b>	<b>2.80 (1.96–4.01)</b>	<b>0.40 (0.15–0.64)</b>

Significant HRs are in bold.

\*Adjusted for gender.

†Adjusted for gender, educational status, body mass index, physical activity and cardiovascular disease

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

performed analyses restricted to drinkers. However, our findings of an inverse dose–response relationship between the amount of alcohol consumption and RA incidence, as well as the synergistic effect between alcohol consumption and smoking remained significant also when non-drinkers were excluded.

No universally accepted classification system exists for low, moderate and high alcohol consumption. Our classification was based on the gender-specific distribution of alcohol at baseline. High alcohol consumption in our study (more than 66 g/week among women or 105 g/week among men) is indeed considered moderate by Statistics Sweden.<sup>22</sup> Relatively few participants in our study reported alcohol intake over the recommended level. We also examined other ways to classify alcohol exposure. However, using the same classification based on the distribution among all participants together, or applying the classification that is used by Statistics Sweden, only marginally changed our results. Several autoimmune diseases have been inversely associated with alcohol consumption, such as systemic lupus erythematosus,<sup>23</sup> autoimmune thyroid diseases,<sup>24 25</sup> type 1 diabetes mellitus<sup>26</sup> and multiple sclerosis.<sup>27</sup> An interaction between drinking and smoking, similar to the one we found for RA, has been observed with regard to risk of multiple sclerosis,<sup>27</sup> another complex Th1 driven inflammatory disease.

Alcohol intake dose-dependently affects innate and adaptive aspects of the immune system.<sup>23</sup> Previous studies have shown an alcohol induced alteration in cytokine

production, where low to moderate alcohol consumption is associated with decreased production of pro-inflammatory cytokines such as IL-1, IL-6 and TNF.<sup>2 3 28 29</sup> A recently published in vivo study on mice suggested that one mechanism might involve altered function of T-follicular helper cells (T<sub>FH</sub> cells), leading to impaired antibody formation.<sup>29</sup> Alcohol-induced epigenetic changes, resulting in altered gene expression, may also affect immune homeostasis.<sup>30 31 32</sup> However, the specific molecular mechanisms underlying ethanol's impact on RA incidence remain poorly understood; knowledge concerning the molecular mechanisms underlying the specific interaction presented in this study is also limited.

Strengths of this study include its prospective design, large sample size with long-term virtually complete follow-up through linkage to nationwide Swedish registers. Further, the study was performed in the context of the Swedish welfare system with equal access to medical services for all citizens. A possible limitation is the way the recruitment to the study was done, where the volunteers in the study might be healthier than the average population (a healthy volunteer bias). This might explain why the reported alcohol consumption was somewhat lower than expected. However, since many population-based studies struggle with low response rate and incomplete follow-up, the disadvantage of a non-representative sample must be weighed against the increased feasibility of the study, and the completeness of the answers with a remarkably low level of missing data. Although under-reporting alcohol consumption

**Table 5** HR with 95% CI of developing RA among drinkers with different combinations of weekly alcohol consumption and smoking

Alcohol consumption	Ever smoking	N	Person years	Incident RA	HR (95% CI)*	HR (95% CI)†	AP (95% CI)
Moderate-high	No	9001	164 529	87 (1.0)	1.0 (reference)	1.0 (reference)	
Low	No	11 195	198 686	133 (1.2)	1.14 (0.87–1.50)	1.10 (0.84–1.45)	
Moderate-high	Yes	8831	158 256	125 (1.4)	<b>1.37 (1.04–1.80)</b>	<b>1.32 (1.00–1.74)</b>	
Low	Yes	6566	113 202	129 (2.0)	<b>1.94 (1.48–2.55)</b>	<b>1.81 (1.37–2.38)</b>	<b>0.22 (0.02–0.52)</b>

Significant HRs are in bold.

\*Adjusted for gender.

†Adjusted for gender, educational status, body mass index, physical activity and cardiovascular disease.

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

is possible, there is no reason to believe that participants who later developed RA would under-report alcohol to a greater extent. Therefore, differential misclassification of alcohol, as well as smoking, seems unlikely. Since few participants reported high alcohol consumption, according to the classification that is used by Statistics Sweden, we were not able to further analyse whether the inverse dose–response relationship was interrupted at a certain level of alcohol intake, which has been demonstrated previously.<sup>4 11</sup>

Information on smoking habits, alcohol consumption as well as confounders was collected only at study baseline and might have changed during the follow-up. Such misclassification would usually be non-differential and entail attenuation of our risk estimates.

Despite a large number of participants in the cohort, the prevalence of current smokers at baseline was too low for informative analyses by a more detailed characterisation of smoking history. However, when current smokers were excluded, the interaction between smoking and alcohol remained similar. This was expected, since the influence of smoking on RA risk persists during decades after smoking cessation.<sup>33</sup> In turn, this indicates that there is a prolonged state of autoimmunity that precedes the symptom onset in RA<sup>34</sup> and lifestyle habits probably influence the risk of disease long before the clinical onset.

In conclusion, our findings suggest that alcohol consumption is inversely associated with RA incidence, which is in accordance with previous studies. A synergistic effect was observed between drinking and smoking with regard to RA incidence. Further studies are needed to understand the mechanisms behind the findings which may contribute to define ways to achieve protection against RA by other means than alcohol consumption.

#### Author affiliations

<sup>1</sup>Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden

<sup>2</sup>Center of Rheumatology, Academic Specialist Center, Stockholm Health Services, Stockholm, Sweden

<sup>3</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

<sup>4</sup>Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy

<sup>5</sup>Clinical Effectiveness Group, Institute of Health and Society, University of Oslo, Oslo, Norway

<sup>6</sup>Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

<sup>7</sup>Stress Research, Stockholm University, Stockholm University, Stockholm, Sweden

<sup>8</sup>Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden

<sup>9</sup>Center for Obesity, Academic Specialist Center, Stockholm Health Services, Stockholm, Sweden

**Acknowledgements** We want to thank all participants in the Swedish National March Cohort for their valuable contribution. We also thank Saedis Saevarsdottir, Lars Klareskog and Lars Alfredsson for contributing with valuable insights in the specific area and fruitful discussions in the process of forming the manuscript.

**Contributors** AKH: study concept and design, statistical analysis. LH and AKH: drafting of the manuscript. RB and WY: data extraction. WY, RB, YTL, TÅ and H-OA: interpretation of data and critical revision of manuscript. All authors approved the final version of the manuscript to be published.

**Funding** LH was supported by research funding from Academic Specialist Center and a clinical research fund from Stockholm county (ALF-funding). AKH was supported by funding from the Swedish Research Council for health, working life and welfare.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The study was approved by the Regional Ethics Committee in Stockholm and all participants provided written informed consent.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. Please contact corresponding author at [louise.hedenstierna@ki.se](mailto:louise.hedenstierna@ki.se).

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#### ORCID iDs

Louise Hedenstierna <http://orcid.org/0000-0002-8225-3794>

Anna Karin Hedström <http://orcid.org/0000-0002-6612-4749>

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