RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL ARTICLE

Interplay between obesity and smoking with regard to RA risk

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To cite: Hedström AK, Klareskog L, Alfredsson L. Interplay between obesity and smoking with regard to RA risk. *RMD Open* 2019;**5**:e000856. doi:10.1136/rmdopen-2018-000856

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2018-000856).

Received 14 November 2018
Revised 25 March 2019
Accepted 1 April 2019

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ABSTRACT

Objectives Previous studies on rheumatoid arthritis (RA) and body mass index (BMI) have yielded diverging results. We aimed to clarify the influence of BMI on the risk of developing anticitrullinated peptide antibody (ACPA)-positive and ACPA-negative RA by taking into consideration gender, smoking habits and human leukocyte antigen (HLA-DRB1) shared epitope (SE) status.

Methods The present report is based on a Swedish population-based, case–control study with incident cases of RA (3572 cases, 5772 matched controls). Using logistic regression models, overweight/obese subjects were compared with normal weight subjects regarding risk of developing RA, by calculating ORs with 95% CIs.

Results We observed diverging results for women and men. Among women, the risk of both ACPA-positive and ACPA-negative RA increased with increasing BMI, whereas an inverse association was observed among men for ACPA-positive RA. The results were similar regardless if RA onset before or after the age of 55 years was considered. When the analyses were stratified by smoking habits, the influence of BMI on RA risk was mainly restricted to smokers. Among women, a significant interaction was observed between smoking and overweight/obesity with regard to both subsets of RA. No interaction was observed between HLA-DRB1 SE and overweight/obesity with regard to RA risk.

Conclusions The interaction between smoking and obesity regarding risk for RA in women warrants efforts to reduce these risk factors in those at risk for RA. The sex differences concerning the influence of obesity on RA risk merit further studies to verify these results and understand underlying mechanisms.

Key messages

What is already known about this subject?

► Previous studies on body mass index (BMI) and rheumatoid arthritis (RA) risk have yielded conflicting results, whereas smoking repeatedly has been associated with both anticitrullinated peptide antibody (ACPA)-positive and ACPA-negative RA. A potential interaction between the two factors has previously not been investigated.

What does this study add?

► Our study reveals that both ACPA-positive and ACPA-negative RA risk increases with increasing BMI in women and that smoking and overweight/obesity synergistically act to increase the risk of both subsets of RA. Obesity did not increase RA risk in men.

How might this impact on clinical practice?

► Preventive measures in order to reduce obesity and smoking are essential. The findings of sex differences in the influence of obesity on risk for RA is important for future studies on disease mechanisms.

INTRODUCTION

Rheumatoid arthritis (RA) is an immune-mediated inflammatory disease, subclassified into subsets based on presence of anticitrullinated peptide antibody (ACPA).[1 2] Distinct genetic and environmental factors seem to operate in the RA subsets.[3–5] Previous studies on RA and body mass index (BMI) have yielded conflicting results. A systematic review and meta-analysis of 11 studies showed that the relative risk for RA was 1.15 (95% CI 1.03 to 1.29) among overweight subjects and 1.31 (95% CI 1.12 to 1.53) for obese subjects, compared with the reference category of normal weight.[6] A dose–response analysis, based on eight studies, showed a non-linear association between BMI and RA risk.[6] Significant heterogeneity was observed across the studies. A prospective cohort study of females indicated that overweight and obesity increased the risk of both ACPA-positive and ACPA-negative RA, but not among those diagnosed after 55 years of age.[7] Other studies, one of which was based on the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study,[8] analysed women and men separately with diverging results.[8–11] Using a Swedish population-based case–control study, we aimed to further clarify the influence of BMI on the risk of developing ACPA-positive and ACPA-negative RA by taking into consideration gender, age at disease onset, smoking habits and HLA-DRB1 SE status.

METHODS

Study design and study subjects

The present report is based on data from the EIRA, which is a population-based case–control study comprising the general population aged 18–70 years in the middle and southern parts of Sweden.[12] Incident cases of RA were recruited from all hospital-based and most privately run rheumatology units in the study area. All cases were diagnosed by a rheumatologist according to the American College of Rheumatology criteria from 1987.[13] For cases recruited between November 1996 and October 2005, one control per case was randomly selected from the population register, matched by age in 5 year age strata, gender and residential area (EIRA I). For cases recruited between October 2005 and September 2014, two controls per case were selected in order to increase power (EIRA II).

During the study period November 1996–September 2014, completed questionnaires were obtained from 3724 cases and 5935 controls. The response proportion was 94% for the cases and 75% for the controls. For the present report, subjects who could not provide information regarding height, weight or smoking habits were excluded (32 cases and 76 controls). A flow chart presenting the number of study subjects is presented in online supplementary table 1.

Anticitrullinated peptide antibody

Cases provided a blood sample at the clinic in which the case was entered. ACPA were measured as anti-human leukocyte antigen (anti-CCP2) IgG using the commercial Immunoscan-RA MARK 2 ELISA test (Euro-Diagnostica AB, Malmö, Sweden). All anti-CCP2 tests were carried out at Karolinska Institutet. According to the manufacturer's instructions, an antibody level exceeding 25 AU/mL was regarded as ACPA positivity. ACPA status was missing for 42 cases, and these were excluded.

Genotyping

Blood samples were available for 3282 cases (88%) and 2793 controls (47%). HLA-DRB1 genotypes were obtained as previously described.[14] The HLA-DRB1*01, HLA-DRB1*04 and HLA-DRB1*10 alleles were classified as the SE alleles.

Data collection and definition of exposure variables

Information regarding lifestyle factors and different exposures was collected using a standardised questionnaire. BMI was calculated by dividing self-reported weight in kilograms by self-reported height in metres squared and categorised into normal weight (18.5–24.99 kg/m^2), overweight (25–30 kg/m^2) or obese (>30 kg/m^2). Subjects with low BMI (<18.5 kg/m^2) were excluded since underweight may indicate other preclinical conditions. Information on smoking was obtained by asking about current and previous smoking habits. Smoking habits were only considered prior to disease onset in the cases and during the same period of time in the corresponding controls. Smoking was dichotomised into ever-smokers or never smokers.

Ancestry, educational level and alcohol consumption were considered potential confounding variables. Assessment of ancestry was based on whether the subject was born in Sweden or not and whether either of the subject's parents had immigrated to Sweden. A subject who was born in Sweden, whose parents had not immigrated, was classified as Swedish. Educational level was dichotomised into those who had a university degree and those who had not. Alcohol consumption was categorised into non-drinking, low consumption (below or equal to the median among controls), moderate consumption (above the median but below or equal to the 75th percentile) or high consumption (above the 75th percentile).

Statistical analysis

Using unconditional logistic regression,[15] the occurrence of ACPA-positive and ACPA-negative RA in overweight and obese subjects was compared with that in normal weight subjects by calculating OR with 95% CI with adjustment for the age, residential area and sex when appropriate. Trend test for a dose–response relationship regarding BMI and risk of ACPA-positive and ACPA-negative RA was performed by using a continuous variable for BMI in a logistic regression model. The analyses were performed separately for women and men and further stratified by smoking habits. We investigated a potential interaction between smoking and overweight/obesity with regard to ACPA-positive and ACPA-negative RA. The interaction was analysed using departure from additivity of effects as criterion of interaction and was evaluated by calculating the attributable proportion due to interaction (AP) together with 95% CIs. With regard to ACPA-positive RA, we also investigated a potential interaction between HLA-DRB1 SE and overweight/obesity.

All analyses were adjusted for age, residential area, ancestry, study and when appropriate gender. The analyses were further adjusted for educational level and alcohol consumption, but these factors had no influence on the results and were not kept in the final analyses. All analyses were conducted using Statistical Analysis System (SAS) V.9.4.

RESULTS

Our analyses of BMI and RA risk included 3572 cases and 5772 matched controls. Among both cases and controls, a higher proportion of men were classified as overweight or obese than women. Among both ACPA-positive and ACPA-negative cases, but not among controls, smoking was significantly more common among those who were overweight or obese than among normal weight subjects. Characteristics of cases and controls, by BMI status, are presented in table 1.

Among women, the risk of both ACPA-positive and ACPA-negative RA increased with increasing BMI (p values for trend 0.009 for ACPA-positive RA and 0.001

Table 1 Characteristics of cases and controls

	Cases	Controls
Women, n (%)	2547 (71)	4122 (71)
Men, n (%)	1025 (29)	1650 (29)
Swedish, n (%)	3001 (84)	4745 (82)
Overweight, n (%)	1239 (35)	1978 (34)
Obesity, n (%)	521 (15)	741 (13)
Smoking, n (%)	2393 (67)	3184 (55)
University degree, n (%)	941 (26)	1742 (30)
Alcohol drinkers, n (%)*	2733 (77)	4745 (82)
Total, n	3572	5772
Age at disease onset (SD)	52.1 (13.0)	
Duration between disease onset and inclusion in the study (SD)	0.9 (1.3)	

*Alcohol drinkers were those who consumed alcohol at the time of the index year.

for ACPA-negative RA), whereas an inverse association was observed among men with regard to ACPA-positive RA (p value for trend 0.009) (table 2). The results were similar regardless if RA onset before or after the age of 55 years was considered (online supplementary tables 2 and 3).

When the analyses were further stratified by smoking habits, the influence of BMI on RA risk was mainly restricted to smokers. Among obese female smokers, the OR of ACPA-positive and ACPA-negative RA was 1.6 (95% CI 1.3 to 2.0) and 2.1 (95% CI 1.6 to 2.8), respectively, compared with normal weight female smokers. The p values for trend were less than 0.0001 (table 3). Among male smokers, obesity decreased the risk of ACPA-positive RA with an OR of 0.5 (95% CI 0.4 to 0.8), whereas no influence of BMI was observed with regard to ACPA-negative RA (table 4). No significant impact of BMI on the risk of ACPA-positive or ACPA-negative RA was observed among never smokers, neither for women nor men (tables 3 and 4).

Among women, a significant interaction was observed between smoking and overweight/obesity with regard to both ACPA-positive RA (AP 0.3, 95% CI 0.1 to 0.4) and ACPA-negative RA (AP 0.3, 95% CI 0.1 to 0.5). Among men, the risk associated with smoking was less pronounced in those who were overweight or obese (table 5).

Table 2 OR with 95% CI of developing ACPA-positive and ACPA-negative RA for overweight and obese subjects compared with normal weight subjects in total and stratified by gender

Total				
	ACPA-positive RA		ACPA-negative RA	
BMI	**Ca/Co***	**OR (95% CI)†**	**Ca/Co***	**OR (95% CI)†**
Normal weight	1231/3053	1.0 (reference)	581/3053	1.0 (reference)
Overweight	798/1978	1.0 (0.9–1.1)	441/1989	1.1 (1.0–1.3)
Obesity	313/741	1.1 (0.9–1.3)	208/741	1.5 (1.2–1.8)
P for trend		0.2		0.002
Women				
	ACPA-positive RA		ACPA-negative RA	
BMI	**Ca/Co***	**Ca/Co***	**Ca/Co***	**OR (95% CI)‡**
Normal weight	944/2426	1.0 (reference)	443/2426	1.0 (reference)
Overweight	506/1196	1.1 (1.0–1.3)	261/1196	1.2 (1.0–1.4)
Obesity	242/500	1.3 (1.1–1.6)	151/500	1.7 (1.4–2.1)
P for trend		0.009		0.001
Men				
	ACPA-positive RA		ACPA-negative RA	
BMI	**Ca/Co***	**Ca/Co***	**Ca/Co***	**OR (95% CI)‡**
Normal weight	287/627	1.0 (reference)	138/627	1.0 (reference)
Overweight	292/782	0.8 (0.6–1.0)	180/782	1.0 (0.8–1.3)
Obesity	71/241	0.6 (0.5–0.8)	57/241	1.1 (0.8–1.5)
P for trend		0.009		0.9

*Number of exposed cases and controls.
†Adjusted for age, gender, residential area, ancestry and study.
‡Adjusted for age, residential area, ancestry and study.
ACPA, anticitrullinated peptide antibody; BMI, body mass index; RA, rheumatoid arthritis.

Table 3 OR with 95% CI of developing ACPA-positive and ACPA-negative RA for overweight and obese women compared with normal weight women stratified by smoking habits

	ACPA-positive RA		ACPA-negative RA	
BMI	Ca/Co*	Ca/Co*	Ca/Co*	OR (95% CI)†
Never smokers				
Normal weight	327/1089	1.0 (reference)	186/1089	1.0 (reference)
Overweight	156/541	1.0 (0.8–1.3)	98/541	1.1 (0.8–1.4)
Obesity	71/268	1.0 (0.7–1.3)	55/268	1.3 (0.9–1.8)
P for trend		0.8		0.8
Ever-smokers				
Normal weight	617/1337	1.0 (reference)	257/1337	1.0 (reference)
Overweight	350/655	1.2 (1.0–1.4)	163/655	1.3 (1.0–1.6)
Obesity	171/232	1.6 (1.3–2.0)	96/232	2.1 (1.6–2.8)
P for trend		<0.0001		<0.0001

*Number of exposed cases and controls.
†Adjusted for age, gender, residential area, ancestry and study.
ACPA, anticitrullinated peptide antibody; BMI, body mass index; RA, rheumatoid arthritis.

No interaction was observed between HLA-DRB1 SE and overweight/obesity with regard to RA risk (online supplementary table 4).

DISCUSSION

We demonstrate a complex interplay between BMI and smoking with regard to RA risk. Among women the risk of both ACPA-positive and ACPA-negative RA increased with increasing BMI, whereas an inverse association between BMI and ACPA-positive RA was observed among men. The results were similar regardless if RA onset before or after the age of 55 years was considered. In women, an interaction was observed between smoking and overweight/obesity concerning risk of both ACPA-positive and ACPA-negative RA, whereas the influence of smoking was attenuated among overweight and obese men, compared with normal weight men. Overweight and obesity had no significant impact on RA risk in women or men who had never smoked.

A subgroup meta-analysis has shown that the risk of RA associated with obesity is higher in females compared with mixed populations,[6] which is in accordance with our findings. The observation of an inverse association between overweight/obesity and ACPA-positive RA among men is in accordance with two nested case–control studies based on prospective health surveys.[11] There are sex differences

Table 4 OR with 95% CI of developing ACPA-positive and ACPA-negative RA for overweight and obese men compared with normal weight men stratified by smoking habits

	ACPA-positive RA		ACPA-negative RA	
BMI	Ca/Co*	Ca/Co*	Ca/Co*	OR (95% CI)†
Never smokers				
Normal weight	63/116	1.0 (reference)	48/116	1.0 (reference)
Overweight	56/133	0.9 (0.6–1.3)	59/133	1.1 (0.7–1.7)
Obesity	16/35	0.9 (0.5–1.6)	14/35	0.8 (0.4–1.6)
P for trend		0.97		0.8
Ever-smokers				
Normal weight	208/162	1.0 (reference)	78/162	1.0 (reference)
Overweight	210/235	0.7 (0.6–0.9)	104/235	1.0 (0.7–1.3)
Obesity	51/77	0.5 (0.4–0.8)	39/77	1.2 (0.8–1.8)
P for trend		0.003		0.98

*Number of exposed cases and controls.
†Adjusted for age, gender, residential area, ancestry and study.
ACPA, anticitrullinated peptide antibody; BMI, body mass index; RA, rheumatoid arthritis.

Table 5 OR with 95% CI of developing RA for subjects categorised by smoking and BMI status stratified by gender

		ACPA-positive RA		ACPA-negative RA	
Smoking	BMI	Ca/Co*	OR (95% CI)†	Ca/Co*	OR (95% CI)†
Women					
–	18.5–25	327/1089	1.0 (reference)	186/1089	1.0 (reference)
–	>25	227/809	1.0 (0.8 to 1.2)	153/809	1.1 (0.9 to 1.4)
+	18.5–25	617/1337	1.5 (1.2 to 1.7)	257/1337	1.1 (0.9 to 1.3)
+	>25	521/887	2.0 (1.7 to 2.3)	259/887	1.6 (1.3 to 2.0)
			AP 0.3 (0.1 to 0.4)		AP 0.3 (0.07 to 0.5)
Men					
–	18.5–25	71/288	1.0 (reference)	53/288	1.0 (reference)
–	>25	84/402	0.9 (0.6 to 1.2)	78/402	1.0 (0.7 to 1.6)
+	18.5–25	216/339	2.5 (1.8 to 3.4)	85/339	1.2 (0.8 to 1.8)
+	>25	276/621	1.7 (1.3 to 2.3)	159/621	1.2 (0.9 to 1.8)

Attributable proportion due to interaction between smoking and overweight/obesity.
*Number of exposed cases and controls.
†Adjusted for age, residential area, ancestry and study.
ACPA, anticitrullinated peptide antibody; BMI, body mass index; RA, rheumatoid arthritis.

related to obesity, including anatomical adipose tissue distribution, sex hormone effects, receptor activity, genetic influences and inflammatory responses.[16] Obese people have higher levels of oestrogens and androgens that have been shown to play a role in the development of RA. Oestrogen stimulates antibody production and is also involved in the breakdown of B cell tolerance.[17] Our finding that overweight and obesity differently affects the risk of RA among women and men could reflect the sexual dimorphism of obesity and the underlying pathways could be related to sex hormones.

Several mechanisms could explain our finding of an association between overweight/obesity and RA risk in women. Obesity is characterised by a chronic, low-grade systemic inflammation that arises from the production and secretion of inflammatory mediators driven by adipose tissue macrophages.[18] Leptin, mainly produced by adipose tissue in proportion to body fat mass, is an important regulator of inflammation and has been considered a link between obesity, metabolic state and autoimmunity.[19] Increased expression of leptin has been associated with increased susceptibility to a number of inflammatory and autoimmune diseases. Leptin promotes Th1 responses and reduces regulatory T cell responses, thereby promoting the onset and progression of autoimmune responses.[20]

Another potential mechanism for the association between BMI and RA may involve vitamin D status. Total body fat is inversely related to the levels of circulating 25-hydroxyvitamin D, and consequently, obese people have lower levels of this metabolite than normal weight people.[21] Vitamin D deficiency has been associated with multiple autoimmune disorders including RA.[22] The link between obesity and autoimmune diseases could also be driven by a genetic variation that predisposes individuals to both conditions.

Both smoking and overweight/obesity are modifiable lifestyle factors. A public health strategy in Finland aiming at dietary changes and smoking cessation has resulted in a major reduction of cardiovascular diseases,[23] which was accompanied by a similar decline in RA incidence.[24] Such prevention programmes may contribute to the prevention of RA and other diseases associated with lifestyle habits.

Our study was designed as a case–control study, and information regarding environmental exposures and lifestyle habits, such as smoking, was collected retrospectively. We minimised the risk of recall bias by using incident cases of RA. Data on BMI were based on self-reported weight and height. A meta-analysis of 21 studies showed that self-reported weight was underestimated by −0.94 kg, whereas self-reported height was overestimated by 0.36 cm, compared with direct measures.[25] Underestimates or overestimates would probably not differ between cases and controls. However, data on BMI were collected on average 0.9 years after disease onset, which is considered a limitation since BMI may change in early RA.[26 27]

A potential selection bias may arise when recruiting cases and controls. The proportion of respondents with regard to participation in EIRA was 94% for cases and 75% for controls. Since the structure of the Swedish public healthcare system provides equal access to medical services for all Swedish citizens, it is most likely that almost all cases of RA are referred to public rheumatology units, and it is not likely that the few unidentified cases would cause a substantial bias in our calculations. Selection bias among controls is likely to be modest since the prevalence of overweight/obesity and smoking among controls, seen as an indicator of life style, was in line with that of the general population at equivalent ages.[28]

In summary, there is a complex interplay between BMI and smoking with regard to ACPA-positive and

ACPA-negative RA, with a different pattern among women and men. Prevention programmes aiming at dietary changes and smoking cessation may reduce RA incidence.

Contributors Conception and design of the study: all authors. Acquisition of data: LA and LK. Analysis of data and drafting of the manuscript: AKH. All authors interpreted the data and revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Funding The Epidemiological Investigation of Rheumatoid Arthritis study was supported by grants from the Swedish Medical Research Council, the Swedish Council for Health, Working life and Welfare, King Gustaf V:s 80-year foundation, the Swedish Rheumatism Foundation, Stockholm County Council, Swedish Society for Medical Research, the insurance company AFA, and the Innovative Medicines Initiative (IMI)-supported RTCure projects.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data are available upon reasonable request.

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