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Original article

A high body mass index is associated with reduced risk of rheumatoid arthritis in men, but not in women

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Abstract

Objective. To investigate the impact of overweight and obesity on the risk of RA.

Methods. From two large population-based health surveys (30 447 and 33 346 participants), individuals who developed RA after inclusion were identified by linkage to four different registers and a structured review of the medical records. Matched controls were selected from the corresponding health survey database. The impact of overweight or obesity (BMI $>$ 25 kg/m^2) compared with normal BMI (18.5–25 kg/m^2) on the risk of RA was examined in conditional logistic regression models, stratified by sex.

Results. A total of 172 (36 men/136 women) and 290 (151 men/139 women) individuals were diagnosed with RA after inclusion in the two health surveys. The median time from inclusion to RA diagnosis was 5 years and 12 years, respectively. In men, being overweight or obese at inclusion in the health survey was associated with a reduced risk of subsequent development of RA in both cohorts [odds ratio (OR) = 0.33; 95% CI: 0.14, 0.76, and 0.60; 95% CI: 0.39, 0.91]. There was no such association in women (OR = 1.01; 95% CI: 0.65, 1.54, and 1.37; 95% CI: 0.86, 2.18). Estimates were similar in analyses adjusted for potential confounders, including smoking.

Conclusion. A high BMI was associated with a reduced risk of future RA in men, but not in women. Factors related to adipose tissue may contribute to mechanisms that are protective from RA in men.

Key words: rheumatoid arthritis, body mass index, overweight, obesity, predictors.

Rheumatology key messages

- Overweight or obesity was negatively associated with development of RA in men.
- The reduced risk of RA in men with high BMI was not explained by smoking.
- BMI did not significantly affect the risk of RA in women.

Introduction

Risk factors for RA include genetic [1] and environmental factors [2]. Smoking is an established predictor of RA [3]. Recently, several studies have suggested that BMI may influence development of RA as well as the subsequent disease course [4]. There are conflicting reports on the impact of a high BMI on development of RA, with some studies reporting an increased risk in obese individuals, and others finding no such association [2, 5–11]. The majority of studies indicate a positive association between obesity and RA in women [12]. For example, in an analysis from the Nurses' Health Survey, the presence of obesity in women aged $<$55 years was a risk factor for RA [9]. By contrast, there are limited data on the impact of BMI on the risk of RA in men. Wesley *et al*. [11] reported from the Swedish Epidemiological Investigation in RA, a case–control study in which heights and weights before RA onset were based on retrospective self-report, that obesity was associated with reduced risk of ACPA-positive RA in men.

Sex-specific patterns in associations between exposures and RA development may reflect underlying

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CLINICAL SCIENCE

pathways related to sex hormones. This is of particular interest, given the described associations between hormone-related factors and RA in women [13] as well as in men [14].

In retrospective investigations of lifestyle factors and disease risk, there are methodological issues related to recall bias and to the direction of causality. Ideally, assessment of BMI and other exposures should be performed using standardized methods, before onset of symptoms.

The purpose of this study was to examine the effect of overweight and obesity on the risk of RA in a study of men and women who were included in two large population-based health surveys. To our knowledge, this is the first nested case–control study to investigate this issue in men.

Patients and methods

Source populations

This nested case–control study used information from the Malmö Diet Cancer Study (MDCS) and the Malmö Preventive Medicine Program (MPMP), two population-based health surveys performed in Malmö, Sweden, current population 300 000 (during the screening period 1974–96: between 229 000 and 247 000). In both cohorts, the vast majority of participants were Caucasians of Scandinavian origin. All participants gave their written informed consent for inclusion in the MDCS or the MPMP. The current study was approved by the regional research ethics committee for southern Sweden.

The MDCS included 30 447 subjects (12 121 men and 18 326 women) and was performed between 1991 and 1996. Details of recruitment are described elsewhere [15]. The cohort included residents in Malmö—all women born between 1923 and 1950 and all men born between 1923 and 1945. The total source population was 74 138 persons, and the participation rate was 41%. The only exclusion criteria were inadequate Swedish language skills and mental incapacity. Information on lifestyle factors was obtained using a self-administered questionnaire. The mean age at screening was 58 years in women and 59 years in men.

The MPMP was conducted between 1974 and 1992. The programme included a total of 22 444 males born between 1921 and 1949 and 10 902 females born between 1925 and 1938. Details on the recruitment are described elsewhere [16]. Every participant filled out a self-administered questionnaire on medical and personal history. The overall response rate was 71%. During the first half of the period (1974–82), mostly men were invited, and mostly females were invited during the second half (1982–92). The mean age at screening was 49 years in women and 44 years in men.

Exposure information

In both surveys, height and weight were measured in light indoor clothing. Height was measured to the nearest centimetre and weight was recorded at intervals of 0.1 kg. BMI was calculated as weight (in kg)/height^2 (in m^2). Information on smoking, level of formal education and alcohol consumption was obtained using self-administered questionnaires, as previously described [17, 18]. In the MPMP, data on self-reported overall health and self-reported cancer, diabetes and cardiovascular disease (the latter classified as self-report of either hospitalization for stroke, physician diagnosis of angina pectoris or current use of heart medication) at baseline were extracted from the self-administered questionnaire. Data on socioeconomic status of participants in the MPMP was derived from self-reported job titles in the Swedish national censuses, as previously described [17].

Cases and controls

Individuals who developed RA after inclusion in the MDCS or the MPMP, up to 31 December 2004, were identified in each cohort separately, as previously described [17, 18]. Briefly, each cohort was linked to several local and national registers [19–21]. In a structured review of all medical records, possible cases were validated and classified according to the 1987 ACR criteria for RA [22], and the date of RA diagnosis was determined. Only cases with a first documented diagnosis at least 1 year after inclusion in the MDCS or the MPMP were included. Four controls for each validated case, matched for sex, year of birth and year of screening, who were alive, living in Sweden and free of RA when the index person was diagnosed with RA, were selected from the corresponding health survey database. Vital status and information on emigration were retrieved from the national census. Data on RF tests were retrieved from the two clinical immunology laboratories in the area.

The incident cases of RA that were investigated in this study were identified in a structured review performed in 2005–06. Identification and validation of cases with a first diagnosis of RA after 2004 among participants in the two cohorts is ongoing.

Statistics

Analyses were performed separately for cases and controls from the MDCS and cases and controls from the MPMP. The impact of baseline BMI on the risk of RA was examined in bivariate conditional logistic regression analysis. Each case and the corresponding controls were given a group number, which was entered into the logistic regression models as a categorical variable. ORs per S.D. of BMI were calculated for men and women separately. The risk of RA for individuals fulfilling the WHO criteria for overweight or obesity ($\geqslant$25 kg/m^2), overweight (25–30 kg/m^2) or obesity ($\geqslant$30 kg/m^2), was compared with that for individuals with normal BMI (18.5–25 kg/m^2). The small proportion with a low BMI ($<$18.5 kg/m^2) was excluded from this analysis. To assess potential effect modification, the slopes for the estimates for overweight/obesity in men and women were compared, assuming a normal distribution.

The impact of potential confounders on the risk of RA was examined in a similar manner. Analyses were performed first bivariately and then adjusted for the other

Table 1 Incident cases of RA in the Malmö Diet and Cancer Study and controls

Characteristic n	All		Women		Men	
	Cases 172	Controls 688	Cases 136	Controls 544	Cases 36	Controls 144
Age at inclusion, mean (S.D.), years	58.0 (7.2)	58.0 (7.2)	57.9 (7.3)	58.0 (7.3)	58.5 (6.7)	58.4 (6.7)
Time from inclusion to RA diagnosis, median (IQR), years	5 (3–8)	NA	5.5 (3–8)	NA	5 (3–8)	NA
Age at diagnosis, mean (S.D.) (range), years	63.4 (8.0) (47–80)	NA	63.3 (8.2) (47–80)	NA	63.9 (7.1) (50–77)	NA
RF positive at diagnosis or later, n (%)	114 (66)	NA	90 (66)	NA	24 (67)	NA
Current smokers at inclusion, n (%)	62 (36)	177 (26)	48 (35)	148 (27)	14 (39)	29 (20)
Low level of formal education,[a] n (%)	78 (49)	262 (40)	66 (51)	206 (40)	12 (40)	56 (42)
Infrequent alcohol consumption,[b] n (%)	32 (20)	58 (9)	29 (23)	52 (10)	3 (10)	6 (5)
Recent alcohol consumption,[b] n (%)	112 (70)	521 (80)	85 (65)	404 (78)	27 (87)	117 (87)
Abstainers,[b] n (%)	17 (11)	70 (11)	16 (12)	59 (12)	1 (3)	11 (8)
BMI, mean (S.D.), kg/m^2	25.7 (4.6)	25.8 (4.2)	25.9 (4.9)	25.6 (4.4)	24.6 (3.1)	3.5 (26.5)
Normal BMI, 18.5–25 kg/m^2, n (%)	89 (52)	324 (47)	68 (50)	272 (50)	21 (58)	52 (36)
Overweight/obese, >25 kg/m^2, n (%)	82 (48)	357 (52)	67 (50)	265 (49)	15 (42)	92 (64)
Overweight, 25–30 kg/m^2, n (%)	56 (33)	251 (36)	44 (33)	182 (34)	14 (39)	69 (48)
Obese, >30 kg/m^2, n (%)	24 (14)	106 (15)	23 (17)	83 (15)	1 (3)	23 (16)

Characteristics and life style factors, stratified by sex. Data are from the time of screening in the health survey, except when otherwise indicated. [a]⩽8 years of school. [b]Self-reported alcohol consumption during the last year—infrequent: within last year but not last month; recent: within last month; abstainer: no alcohol last year. IQR: Interquartile range; n: number; NA: not applicable.

risk factors in multivariate analysis. In addition, analyses were stratified by RF status at diagnosis or later (ever positive *vs* negative) and also by time from screening to RA diagnosis (above *vs* below the median), in the MPMP and the MDCS separately. Statistical significance was set at $P < 0.05$ (two-sided test). For cases who participated in both the MPMP and the MDCS before being diagnosed with RA, the change in BMI between the two assessments was determined, and mean changes per year, with 95% CIs, were calculated separately for men and women.

Results

Incident cases and controls

A total of 172 patients (36 men/136 women) were diagnosed with RA after inclusion in the MDCS (Table 1). The median time from inclusion to RA diagnosis was 5 years (range 1–13).

In the MPMP, a total of 290 cases of incident RA (151 men/139 women) were identified. The median time from participation in the survey to RA diagnosis was 12 years (range 1–28 years). There were no substantial differences in ESR or self-reported health between cases and controls based on data collected as part of the survey (Table 2). The time to RA diagnosis was similar for male and female cases in both the MDCS (Table 1) and the MPMP (Table 2).

Impact of overweight/obesity and potential confounders

Being overweight or obese at inclusion in the MDCS was associated with a reduced risk of subsequent development of RA in men (OR = 0.33; 95% CI: 0.14, 0.76), but not in women (OR = 1.01; 95% CI: 0.65, 1.54). A similar association was demonstrated for men in the MPMP (OR = 0.60; 95% CI: 0.39, 0.91), whereas for women in the MPMP with overweight/obesity, the OR for developing RA was 1.37 (95% CI: 0.86, 2.18). The slope for the estimate of the impact of overweight/obesity was significantly different between men and women in both cohorts ($P = 0.02$ in the MDCS; $P = 0.01$ in the MPMP). Men who fulfilled the WHO definition for obesity (BMI > 30 kg/m^2) had a significantly decreased risk of RA compared with those with normal BMI in the MDCS (Table 3). Overweight (BMI 25–30 kg/m^2) was associated with a significantly reduced risk of RA in the MPMP (Table 4) and there was a similar trend in the MDCS (Table 3). In analyses using BMI as a continuous variable, the risk of RA decreased significantly with increasing BMI in men, but not in women (Tables 3 and 4).

Table 2 Incident cases of rheumatoid arthritis and controls in the Malmö Preventive Medicine Project

Characteristic n	All		Women		Men	
	Cases 290	Controls 1160	Cases 139	Controls 556	Cases 151	Controls 604
Age at inclusion Mean (S.D.), years	47.1 (7.1)	47.1 (7.1)	49.3 (7.4)	49.3 (7.4)	45.5 (6.2)	45.5 (6.2)
Time from inclusion to RA diagnosis Median (IQR), years;	12 (8–18)	NA	11 (7–16)	NA	13 (9–19)	NA
Age at diagnosis Mean (S.D.) (range), years	59.9 (8.8; 30–81)	NA	60.8 (8.4; 30–76)	NA	59.1 (9.0; 40–81)	NA
RF positive at diagnosis or later, n/total (%)	179/250 (71.6)	NA	86/128 (67.2)	NA	93/122 (76.2)	NA
Current smokers at inclusion, n (%)	155 (53.8)	486 (42.9)	64 (46.0)	197 (35.4)	91 (60.3)	289 (47.8)
Ever smokers at inclusion, n/total (%)	181/260 (69.6)	625/1037 (60.3)	25/139 (61.2)	295/553 (53.3)	96/121 (79.3)	330/484 (68.2)
Blue-collar worker, n (%)	146 (50.3)	496 (42.8)	67 (48.2)	230 (41.4)	79 (52.3)	266 (44.0)
White-collar worker, n (%)	107 (36.9)	511 (44.1)	55 (39.6)	253 (45.5)	52 (34.4)	258 (42.7)
BMI, mean (S.D.), kg/m^2	24.3 (3.5)	24.7 (3.7)	24.3 (4.1)	24.3 (4.3)	24.3 (2.7)	25.0 (3.3)
Normal BMI[a], n (%)	165 (56.9)	640 (55.2)	75 (54.0)	333 (59.9)	90 (59.6)	307 (50.8)
Overweight/obese[b], n (%)	115 (39.7)	498 (42.9)	58 (41.7)	206 (37.1)	57 (37.7)	292 (48.3)
Overweight[c], n (%)	98 (33.8)	410 (35.3)	47 (33.8)	149 (26.8)	51 (33.8)	261 (43.2)
Obese[d], n (%)	17 (5.9)	88 (7.6)	11 (7.9)	57 (10.3)	6 (4.0)	31 (5.1)
ESR, median (IQR), mm	6 (4–11)	6 (4–10)	9 (5–14)	8 (5–12)	5 (3–8)	4 (3–7)
Full self-reported health, n/total (%)	208/290 (72)	795/1155 (69)	99/139 (71)	364/551 (66)	109/151(72)	431/604 (71)
Self-reported cancer, n/total (%)	8/260 (3)	28/1037 (3)	6/139 (4)	27/553 (5)	2/121 (2)	1/484 (0.2)
Self-reported diabetes, n/total (%)	12/259 (5)	35/1036 (3)	9/138 (6)	25/562 (4)	3/121 (2)	10/484 (2)
Self-reported cardiovascular disease, n/total (%)	8/260 (3)	27/1037 (3)	6/139 (4)	20/553 (4)	2/121 (2)	7/484 (1)

Characteristics and metabolic factors, stratified by sex. Data are from the time of screening in the health survey, except when otherwise indicated. [a]BMI: 18.5–25 kg/m^2. [b]BMI $\geqslant$25 kg/m^2. [c]BMI: 25–30 kg/m^2. [d]BMI $>$30 kg/m^2. IQR = Interquartile range; NA = not applicable; n = number.

Table 3 Predictors of RA in the Malmö Diet and Cancer Study—stratified by sex Bivariate conditional logistic regression

Parameter	Men, OR (95% CI)	Women, OR (95% CI)
Smoking		
No current smoking	1.00 (reference)	1.00 (reference)
Current smoking	3.35 (1.32, 8.48)	1.68 (1.05, 2.69)
Level of formal education		
University degree	1.00 (reference)	1.00 (reference)
$\leqslant$8 years of school	3.59 (0.56, 17.1)	2.32 (1.05, 5.14)
Alcohol consumption[a]		
Infrequent	1.00 (reference)	1.00 (reference)
Recent	0.32 (0.04, 2.35)	0.28 (0.14, 0.52)
Abstainer	0.09 (0.01, 1.88)	0.38 (0.16, 0.90)
BMI		
Normal BMI (18.5–25 kg/m^2)	1.00 (reference)	1.00 (reference)
Overweight/obese ($>$25 kg/m^2)	0.33 (0.14, 0.76)	1.00 (0.65, 1.54)
Overweight (25–30 kg/m^2)	0.42 (0.17, 1.00)	0.95 (0.59, 1.53)
Obese ($>$30 kg/m^2)	0.08 (0.01, 0.67)	1.12 (0.61, 2.05)
BMI, per S.D.	0.47 (0.29, 0.76)	1.09 (0.89, 1.35)

[a]Self-reported alcohol consumption during the last year. Infrequent: within last year but not last month; Recent: within last month; Abstainer: No alcohol last year. OR: odds ratio.

Smoking was a predictor of RA in both sexes in the MDCS (Table 3) and in the MPMP (Table 4), and was negatively associated with overweight/obesity in men [OR = 0.44 (95% CI: 0.22, 0.88) in the MDCS; 0.67 (95% CI: 0.50, 0.94) in the MPMP]. There was a similar relation between smoking and overweight/obesity in women included in the MPMP (OR = 0.65; 95% CI: 0.46, 0.97), whereas there was no significant association between smoking and overweight/obesity in women in the MDCS (OR = 0.83; 95% CI: 0.60, 1.16). A low level of formal education ($\leqslant$ 8 years

Table 4 Predictors of RA in the Malmö Preventive Medicine Project—stratified by sex Bivariate conditional logistic regression

Parameter	Men, OR (95% CI)	Women, OR (95% CI)
Smoking		
No current smoking	1.00 (reference)	1.00 (reference)
Current smoking	1.97 (1.29, 3.02)	1.61 (1.04, 2.49)
Socio-economic status		
White-collar worker	1.00 (reference)	1.00 (reference)
Blue-collar worker	1.63 (1.05, 2.53)	1.45 (0.97, 2.27)
BMI		
Normal BMI (18.5–25 kg/m^2)	1.00 (reference)	1.00 (reference)
Overweight/obese (>25 kg/m^2)	0.60 (0.39, 0.91)	1.37 (0.86, 2.18)
Overweight (25–30 kg/m^2)	0.59 (0.39, 0.92)	1.57 (0.96, 2.57)
Obese (>30 kg/m^2)	0.62 (0.23, 1.70)	0.85 (0.38, 1.88)
BMI, per S.D.	0.72 (0.58, 0.89)	1.02 (0.84, 1.28)

OR: odds ratio.

Table 5 Impact of BMI and obesity/overweight on the risk of RA in the MDCS and the MPMP

Parameter	MDCS, OR (95% CI)		MPMP, OR (95% CI)	
	Adjusted for smoking	Fully adjusted model[a]	Adjusted for smoking	Fully adjusted model[b]
Men				
Normal BMI (18.5–25 kg/m^2)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight/obese (>25 kg/m^2)	0.37 (0.16, 0.87)	0.37 (0.13, 1.04)	0.60 (0.39, 0.92)	0.74 (0.46, 1.17)
Overweight (25–30 kg/m^2)	0.47 (0.19, 1.14)	0.44 (0.15, 1.29)	0.62 (0.39, 0.95)	0.75 (0.46, 1.20)
Obese (>30 kg/m^2)	0.09 (0.01, 0.80)	0.14 (0.01, 1.44)	0.52 (0.18, 1.52)	0.64 (0.20, 2.02)
BMI; per S.D.	0.51 (0.32, 0.83)	0.58 (0.33, 1.04)	0.74 (0.60, 0.92)	0.66 (0.41, 1.07)
Women				
Normal BMI (18.5–25 kg/m^2)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight/obese (>25 kg/m^2)	1.01 (0.65, 1.55)	0.96 (0.60, 1.53)	1.40 (0.87, 2.27)	1.45 (0.85, 2.47)
Overweight (25–30 kg/m^2)	0.94 (0.58, 1.53)	0.96 (0.57, 1.61)	1.60 (0.96, 2.67)	1.67 (0.94, 2.69)
Obese (>30 kg/m^2)	1.05 (0.63, 2.11)	0.96 (0.48, 1.92)	0.90 (0.40, 2.01)	0.90 (0.36, 2.26)
BMI, per S.D.	1.11 (0.89, 1.38)	1.08 (0.86, 1.36)	1.05 (0.83, 1.33)	1.02 (0.78, 1.33)

Multivariate conditional logistic regression. [a]Adjusted for smoking, level of formal education and alcohol consumption. [b]Adjusted for smoking and socio-economic status (blue-collar worker *vs* white-collar worker). OR: odds ratio; MDCS: Malmö Diet and Cancer Study; MPMP: Malmö Preventive Medicine Project.

compared with university degree) predicted RA in the MDCS (Table 3), and was associated with overweight/obesity in women (OR = 2.92; 95% CI: 1.72, 4.99), but there was no significant association in men (OR = 1.48; 95% CI: 0.57, 3.84). In the MPMP, blue-collar workers of both sexes were more likely to develop RA (Table 4), and blue-collar workers were more likely than white-collar workers to be overweight/obese among women (OR = 1.42; 95% CI: 1.02, 1.99), whereas there was no significant association in men (OR = 1.25; 95% CI: 0.92, 1.71). Self-reported recent alcohol consumption was associated with reduced risk of RA, in particular for women (Table 3). There was a trend towards an association between recent alcohol consumption and overweight/obesity in men (OR = 2.80 compared with infrequent alcohol consumption; 95% CI: 0.67, 11.6), but not in women (OR = 1.11; 95% CI: 0.69, 1.78).

Overweight/obesity and RA—multivariate analyses

Since smoking was a significant predictor of RA in both sexes, and negatively associated with overweight/obesity in men, analyses of the impact of overweight/obesity on the risk of RA were adjusted for smoking. Again, there was a significant association in men between having a BMI > 25 kg/m^2 and reduced risk of subsequent development of RA [adjusted ORs = 0.37; 95% CI: 0.16, 0.87 in the MDCS; 0.60 (95% CI: 0.39, 0.92) in the MPMP], with a particularly strong negative association in those who fulfilled the definition for obesity in the MDCS (Table 5). The estimated impact of overweight/obesity on the risk of RA in men was similar in analyses adjusted for smoking, level of education and alcohol use in the MDCS and in analyses adjusted for smoking and socio-economic status in the MPMP (Table 5). In women, overweight/

obesity had no significant effect on the risk of RA in multivariate analyses (Table 5).

Stratified analysis

In men, the estimated impact of overweight/obesity, adjusted for smoking, was similar for RF-positive RA and RF-negative RA in the MDCS [adjusted ORs with 95% CI: 0.33 (0.12, 0.94) and 0.38 (0.03, 4.19), respectively] and the MPMP [adjusted ORs with 95% CI: 0.66 (0.39, 1.14) and 0.64 (0.26, 1.56), respectively]. In women, overweight/obesity was associated with a reduced risk of RF-negative RA in the MDCS (smoking-adjusted OR = 0.41; 95% CI: 0.19, 0.92), but not in the MPMP (smoking-adjusted OR = 1.13; 95% CI: 0.48, 2.67). Overweight/obesity did not significantly affect the risk of RF-positive RA in women in the MDCS (smoking-adjusted OR = 1.52; 95% CI: 0.19, 2.61) or the MPMP (smoking-adjusted OR = 1.41; 95% CI: 0.78, 2.53).

In analyses stratified by the median time from inclusion in the MDCS/MPMP to RA diagnosis (1–5 years *vs* 5–12 years in the MDCS; 1–12 years *vs* 13–28 years in the MPMP), the negative association between overweight/obesity and RA development reached significance in smoking-adjusted analysis of men in the MDCS with $\leqslant 5$ years to RA diagnosis and their controls (adjusted OR = 0.21; 95% CI: 0.06, 0.73), but not in the subgroup with longer time to diagnosis (adjusted OR = 0.65; 95% CI: 0.19, 2.26). The corresponding adjusted ORs in the MPMP were 0.66 (95% CI: 0.39, 1.14) for those with $\leqslant 12$ years to RA diagnosis and 0.64 (95% CI: 0.26, 1.56) for those with >12 years to RA diagnosis. Overweight/obesity had no significant impact on the risk of RA in women in either of the strata based on time to RA diagnosis, in the MDCS or the MPMP (data not shown).

Changes in BMI from the MPMP to the MDCS in pre-RA cases

For pre-RA cases who participated in both surveys ($n = 79$; 24 men and 55 women), the mean time between BMI measurements was 12.4 years in men and 8.7 years in women. Among these subjects, there was on average a slight decrease over time in BMI in men (mean change $-0.06\,kg/m^2$ per year; 95% CI: -0.27 to 0.15) and a slight increase in women (mean change $0.14\,kg/m^2$ per year; 95% CI: -0.25 to 0.53).

Discussion

In these nested case–control studies, based on two prospective health surveys, men who were overweight or obese were less likely to develop RA in the future compared with those with a normal BMI. In contrast, BMI had no significant effect on RA development in women, although a modestly increased risk of RA in women with overweight cannot be excluded based on the present results.

Since these patterns were unchanged in analyses adjusted for potential confounders (smoking and either level of education and alcohol intake, or socio-economic status), it is unlikely that they are explained by such exposures. In the MPMP, rates of self-reported key comorbidities were low and similar in cases and controls. Still, residual confounding by other factors is a possibility. BMI is a rather crude measure of metabolic status, and it may reflect underlying lifestyle-related associations with physical activity, dietary habits etc. For example, two recent prospective studies indicate that consumption of sugar-sweetened soft drinks [23] and salt intake [24] may affect the risk of RA.

Although the disease process may start long before the clinical onset of RA, as reflected by the detection of RA-specific antibodies in a small subset 10 years before diagnosis [25, 26], and elevated pro-inflammatory cytokines before disease onset in some cases [27], it is not likely that inflammation-associated weight loss in male pre-RA cases explains the present results. First, although the estimated effect of overweight/obesity was strongest among those included in the MDCS $\leqslant 5$ years before RA diagnosis, a similar pattern was noted among those included in the MPMP 13–28 years before RA diagnosis. Second, among cases who were included in both health surveys before RA diagnosis, there was no major change in BMI over time. Third, in pre-RA cases included in the MPMP, baseline ESR levels were low and comparable with those of controls who did not get RA. Finally, inflammation-associated weight loss in the pre-clinical phase would be expected to affect not only men, but also women.

A recent meta-analysis found an overall association between obesity and increased risk of RA [12]. A subanalysis showed a significant association in female subjects. No such analysis of men was included, probably due to the limited amount of data available. The sex difference in the impact of BMI on the risk of RA in the present study is of interest and intriguing. Our results are compatible with those of Wesley *et al*. [11], who reported a reduced risk of ACPA-positive RA in obese men, and a neutral effect of obesity on ACPA-positive RA in women. On the other hand, the association between obesity and ACPA-negative RA in women reported by Wesley *et al*. remains unexplained, but may illustrate methodologic differences from the present study.

Geographic factors may explain the discrepancy between our study and several studies from the USA that reported an increased risk of RA in obese women [8, 9]. Differences in the distribution of BMI between Scandinavian and US populations may have contributed to this. Since the present study included middle-aged and older women, a particular effect of high BMI in young women, as described in the Nurses' Health Survey [9], would not be detected.

A high BMI more often reflects increased abdominal obesity or increased visceral fat in men compared with women [28], suggesting that the observations in this study may be due to a protective effect of abdominal or visceral fat against the development of RA. Possible

mediators of this effect could be components produced by adipose tissue, such as adipokines, which may play a role in the pathophysiology of RA [29, 30].

The relation between hormonal factors associated with RA [13, 14, 31] and body fat distribution requires further investigation. We previously reported that a negative association between testosterone levels, partly due to hypogonadism, and subsequent RA development in men reached significance only in models adjusted for BMI [14]. In that study, a high BMI was associated with reduced testosterone levels [14], similar to other reports [32]. This suggests that whereas a low testosterone that is due to impaired production (hypogonadism) is a risk factor for RA, increased conversion of androgens to oestrogen in adipose tissue [33] may be associated with a lower risk of RA. Again, this implicates a protective effect of hormonally active adipose tissue against RA.

We recently reported, using similar methodology, a negative association between overweight/obesity and development of GCA, particularly in women [34]. The distinct patterns in analyses stratified by sex suggest different metabolic pathways in the pathogenesis of RA and GCA.

Limitations of this study include the lack of longitudinal data on BMI in the majority of cases. We cannot assess the impact of changes in BMI over time on the risk of RA, although the available data from individuals with repeated BMI assessment suggest that changes were limited. If subjects changed their weight during the relatively long time from the inclusion in the survey to RA diagnosis, this could lead to some degree of misclassification. In addition, since the analyses were based on BMI measured between 1974 and 1992 in the MPMP, and between 1991 and 1996 in the MDCS, and cases diagnosed with RA through 2004, effects of recent secular trends in the distribution of BMI and related exposures in the population would not be identified. However, the negative association between overweight/obesity and RA development in men was if anything stronger in the later survey. Still, further studies should include data on BMI from more recent health surveys, and on cases with RA onset in the last few years.

The number of individuals with obesity in the present study was limited. Based on the available data, the effect of obesity on the risk of RA did not appear to be substantially different from that of overweight. However, a differential effect of very high BMI cannot be ruled out.

Another limitation is the lack of data on ACPA status after diagnosis, which is due to the fact that the majority of patients were diagnosed before routine ACPA analysis was available. However, we did have data on RF, and RF positivity and ACPA positivity are known to have a major overlap in patients with RA [35]. The negative association between overweight/obesity and RF-negative RA in women included in the MDCS should be interpreted with caution, as this pattern was only seen in a subgroup analysis of one of the cohorts. There did not appear to be a differential effect for RF-positive and RF-negative RA in men.

Finally, the lack of information on family history of RA or on specific genetic factors is a limitation of this study. Effects of genetic factors on BMI and RA susceptibility also have the potential to confound the results.

Major strengths include the study design, with exposures measured before RA diagnosis in a standardized manner. The inclusion of a relatively large sample of men who subsequently developed RA is a unique asset of this study. The population-based approach, with a high participation rate in the health surveys, indicates that our cases were representative of patients with RA in the area. On the other hand, the cases were mainly Caucasians of Scandinavian heritage, and the results may not apply to other ethnic groups or other geographic settings.

In conclusion, there was a significantly reduced risk of future RA in men who were overweight or obese, whereas no such pattern was found in women. These findings implicate metabolic pathways related to adipose tissue and hormone-related factors in the development of RA. Investigation of adipokines and other biomarkers in male and female pre-RA subjects and their association with hormone-related exposures may shed further light on the pathogenesis of RA.

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