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TITLE

Body fat percentage, waist circumference and obesity as risk factors for rheumatoid arthritis – a Danish cohort study

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ABSTRACT

Objectives: To investigate the relationship between bioimpedance-derived total body fat percentage, waist circumference (WC) and Body Mass Index (BMI) and the subsequent development of rheumatoid arthritis (RA).

Methods: A population-based prospective cohort study among 55,037 persons enrolled into the Danish Diet, Cancer and Health cohort. Baseline data included anthropometric measures and lifestyle factors. Persons who developed RA were identified through linkage with the Danish National Patient Registry. The relationships between bioimpedance-derived body fat percentage, WC, BMI and incident RA were assessed using Cox proportional hazards regression models, stratifying by gender. All analyses were performed for overall RA and the serological subtypes: 'seropositive RA' and 'other RA'.

Results: A total of 210 men (37.6% seropositive RA) and 456 women (41.0% seropositive RA) developed RA during a median follow-up of 20.1 years. In women, overall RA risk was 10% higher for each 5% increment of total body fat (Hazard Ratio (HR) 1.10; 95% CI 1.02-1.18), 5% higher for each 5cm increment of WC (HR 1.05; 95% CI 1.01-1.10) and nearly 50% higher in those with an obese compared to normal BMI (HR 1.46; 95% CI 1.12-1.90). These positive associations were also found for 'other RA'. In men, there were no clear associations between body fat percentage, WC, or BMI and RA. No significant associations were found for 'seropositive RA' in women or men, possibly related to low sample size.

Conclusions: In women, higher body fat percentage, higher waist circumference and obesity were associated with higher risk of RA.

Significance & Innovations

- Bioelectrical impedance is more sensitive measurement of body composition than body mass index.
- In women, higher bioimpedance-derived body fat percentage, waist circumference and obesity were associated with higher risks of developing RA.
- No clear associations were found between body fat percentage, waist circumference or obesity and risk of developing RA in men.
- Our findings imply that future investigations on potential risk factors for RA should be performed separately for men and women.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammation of synovial joints leading to irreversible joint damage and deformity. The etiology of RA is considered to be multifactorial and lifestyle factors seem to play an important role for the development of RA in genetically susceptible hosts (1). Smoking is the best-studied and now well-established lifestyle risk factor for RA (2), whereas associations with other lifestyle factors are less clear (3–6).

It is well-known that fat tissue secretes proinflammatory cytokines leading to systemic low-grade inflammation with different fat depots contributing in distinct ways (7–9). Thus, from a biological point of view, excess fat tissue might be associated with the development of inflammatory diseases. However, studies, examining the relationship between Body Mass Index (BMI) and the development of RA show conflicting results (10–23). Some studies have observed positive associations between BMI and risk of developing RA (11,12,15,20,21);

some studies found this association in sero-negative (Rheumatoid Factor (RF) or/and Anti-Citrullinated Protein Antibody (ACPA) negative) RA (15,19,20,22); and one study found the association in sero-positive (RF and/or ACPA positive) RA (20).

In all previous studies, BMI has been the preferred measure. However, BMI correlates only modestly with total body fat and does not reflect the fat distribution (24,25). Today, several techniques for estimating total body fat are available, including bioelectrical impedance analysis (BIA), a non-invasive way to estimate body fat, fat-free mass and total body water. BIA has been shown to be a valid and more sensitive measurement of body composition than BMI (26,27). Furthermore, waist circumference (WC) describes fat distribution and correlates more strongly with visceral fat than BMI (28–30).

Sero-positive and sero-negative RA differ in their phenotype, susceptibility genes and impact of smoking as a risk factor (2,31). Therefore, it is important to investigate the association between possible risk factors and the development of sero-positive and sero-negative RA separately. However, some patients who are initially sero-negative at presentation, later become sero-positive (32), indicating that this distinction may not be optimal. Thus, reporting associations for three groups: 'overall RA', 'sero-positive RA', and 'other RA' provides the most legitimate way to present the results, where 'other RA' includes patients who were initially sero-negative.

The aim of our study was to examine the relationship between bioimpedance-derived total body fat percentage, WC and BMI and the subsequent development of overall RA, sero-positive RA and other RA.

SUBJECTS AND METHODS

Setting

The study was a population-based prospective cohort study, conducted within the Danish Diet, Cancer and Health cohort (33).

Data sources

The Danish Diet, Cancer and Health cohort. In the period between 1993 and 1997, a total of 160,725 persons aged 50-64 years were invited to participate in the cohort. Eligible cohort participants were born in Denmark, living in the Copenhagen or Aarhus Counties, and had no previous cancer diagnosis recorded in the Danish Cancer Registry (34). All eligible persons received an invitation containing information about the cohort study. In total, 57,053 persons accepted the invitation. Detailed information about lifestyle factors, socioeconomic status, anthropometric measures, including bio-impedance, were collected at enrolment into the cohort. A detailed description of the Danish Diet, Cancer and Health cohort has been published previously (33).

The Danish Civil Registration System contains information about date of birth, place of residence, vital status and migration into or out of Denmark since 1968. The system is continuously updated and ensures complete follow-up regarding vital and migration status of all Danish citizens (35).

The Danish National Patient Registry contains data about all admissions to somatic hospitals in Denmark since 1977 and all out-patient attendances since 1995 (36), including dates of hospital admissions, ward types, discharge diagnoses, dates of all attendances at out-patient clinics, and diagnoses recorded at each attendance. The diagnoses have been classified in accordance with the Danish version of the International Classification of

Diseases 8th edition (ICD-8) until the end of 1993 and thereafter in accordance with the updated version, ICD-10 (37).

The Danish National Prescription Registry contains information about all prescription drugs dispensed at Danish community pharmacies since 1994 (38). The Registry does not include information about drugs dispensed by hospital pharmacies directly to in-patients or out-patients.

Data linkage

The Danish Diet, Cancer and Health cohort baseline data were linked to the Danish Civil Registration System (35) and the Danish National Patient Registry (36) on the 14th October 2016 and to the Danish National Prescription Registry (38) on the 14th December 2016, using the unique Civil Personal Registration (CPR) number. This number is used in all Danish registries enabling data linkage across all of them at the individual level.

Study population

All participants from the Danish Diet, Cancer and Health cohort without a previous RA diagnosis recorded in the Danish National Patient Registry prior to their enrolment into the cohort and who had no missing data on exposure variables or covariates were included in our study. Persons registered with diagnostic codes related to autoimmune diseases other than RA were not excluded.

Exposure

Anthropometric measures were taken in a standardized manner by trained persons at the enrolment into the Danish Diet, Cancer and Health cohort (33,39). The following exposure

variables, describing baseline body characteristics were used in our study: height (cm), weight (kg), BMI (kg/m^2), WC (cm) and bioelectrical impedance-derived total body fat percentage (%).

Height was measured with the participants standing without shoes and was recorded to the nearest 0.5 cm. Weight was measured using a digital scale, with the participants wearing light clothing or underwear, and was recorded to the nearest 100 g. WC was measured at the narrowest part between the lower rib and the iliac crest (the natural waist) or, in case of an indeterminable waist narrowing, halfway between the lower rib and the iliac crest, and was recorded to the nearest 0.5 cm.

For bioelectrical impedance, non-fasting measurements were performed using a four-electrode BIA 101-F device (Akern/RJL, Florence Italy). The bioelectrical impedance method had previously been validated in a Danish population using a four-compartment-model based on measurements of both total body potassium (whole body counting) and total body water (dilutometry) as a gold standard (40).

Outcome

The outcome of interest was the development of RA. Incident RA cases were identified through the Danish National Patient Registry (36). The following ICD-10 codes were used: M05 (sero-positive RA) and M06 (other RA), if recorded as a primary or a secondary diagnosis. Referral diagnoses were not used. Patients, who were registered with one of "M05" diagnostic codes at the first registration, were defined as having sero-positive RA and patients registered with one of "M06" diagnostic codes – as having 'other RA'. After the study entry, no patients were registered with ICD-8 codes for RA in the Danish National Patient Registry. In order to increase the positive predictive value of the RA diagnosis in the

Registry, data were also linked with the Danish National Prescription Registry. Thus, incident RA cases in our study were defined as patients with their first RA diagnosis in the Danish National Patient Registry after the enrolment into the Danish Diet, Cancer and Health cohort, who had subsequently, at least once, redeemed a prescription for a synthetic Disease Modifying Anti-Rheumatic Drug (sDMARD). The following Anatomical Therapeutic Chemical (ATC) codes(41) from the Danish National Prescription Registry were retrieved: Methotrexate (ATC: L01BA01, L04AX03), Sulfasalazine (ATC: A07EC01), Azathioprine (ATC: L04AX01), Hydroxychloroquine (ATC: P01BA02) and Leflunomide (ATC: L04AA13).

Covariates

At the time of enrolment into the Danish Diet, Cancer and Health cohort, the participants completed a comprehensive questionnaire, covering their health, education, occupation, lifestyle and reproductive factors and a semi-quantitative food frequency questionnaire, whose development and validation has been described previously (42,43). The questionnaires were scanned immediately, and missing answers were filled in during an interview at the clinic. Information about smoking status (current, past or never), smoking duration (years), current tobacco consumption (grams per day), and time since smoking cessation (years) were collected. Current tobacco consumption was calculated in grams per day using conversion factors of 1 for cigarettes, 4.5 for cigars and 3 for cheroots or pipe. Dietary information was obtained by a detailed, 192-item food-frequency questionnaire, which study participants had received by mail before their visit to the study clinic. The participants were asked to report their average intake of different food and beverage items over the past 12 months within 12 possible categories ranging from never to 8 times or more per day. Daily intake of specific foods and nutrients was calculated for each participant

using the software program FoodCalc (33), using specifically developed standardized recipes and portion sizes. Alcohol intake was reported for 6 different types of alcoholic beverages: light, regular or strong beer (in bottles), wine (in glasses), fortified wine (in drinks), spirits (in drinks) in predefined categories from never to 8 or more drinks per day. The alcohol content for each type was summed up, and daily amount (gram) of alcohol intake was calculated. Physical activity during the past year was assessed from questions about average number of hours per week spent on leisure-time activities (walking, gardening, housework, home maintenance, sports, biking) and work activities. Physical activity was quantified in Metabolic Equivalent of Task (MET) hours per week. Self-reported length of education was collected in predefined categories (primary school, higher education 1-2 years, higher education 3-4 years, higher education more than 4 years).

Statistical analyses

For descriptive statistics, we reported medians with Interquartile Range (IQR) and percentages for discrete variables separately for men and women. The associations between each exposure (bioimpedance-derived total body fat percentage, WC, BMI) and the development of overall RA, sero-positive RA and other RA were examined using Cox´s proportional hazards regression models with delayed entry and age as the underlying time variables (44) separately for men and women. The dose-response associations were elucidated using Cox regression models with restricted cubic splines.

The participants were followed until development of RA, death, loss to follow-up, or October 2016, whichever came first.

Total body fat percentage was entered into the models as a continuous variable in two ways – per 5% increment in the main analysis and per 1% increment in the dose-response analysis. WC was entered as a continuous and as a categorical variable. As a continuous variable, WC was entered into the models in two ways - per 5cm increment in the main analysis and per 1cm increment in the dose-response analysis. As a categorical variable, WC was grouped into non-abdominal obese and abdominal obese categories, using recommended WHO cut-off values for men/women of >102/>88 cm for abdominal obesity (45,46). BMI was entered as a continuous (per 1-unit kg/m^2 increment) and as a categorical variable. BMI was categorized according to the World Health Organization (WHO) into underweight (<18.5 kg/m^2), normal weight (18.5-24.99 kg/m^2), overweight (25-29.99 kg/m^2) and obese (≥30 kg/m^2) groups (45,46). Non-abdominal obese and normal weight persons were entered as reference groups (45,46). All results were further reported as linear function hazards ratios with 95% confidence intervals (CI).

All analyses were performed stratifying by sex, first as univariate analyses (age-adjusted), then adjusting for age and smoking (status (never, former, current), duration, tobacco g/d) and, finally, as multivariate analyses, adjusting for age, smoking (status, duration, tobacco g/d), alcohol consumption (g/year), educational level (primary school, higher education 1-2 years, higher education 3-4 years, higher education >4 years), overall physical activity, measured as the Metabolic Equivalent of Task (MET, hours per week) (47), and total intake of n-3 fatty acids (g/d), as potential confounders.

Analyses were performed using Stata, version 14.2, College Station, Texas, USA.

RESULTS

A total of 57,053 persons consented to participate in the Danish Diet, Cancer and Health cohort study. Due to the registration delay in the Danish Cancer Registry, 578 persons were erroneously included in the cohort study, as they had been diagnosed with cancer before the enrolment. Among the remaining 56,475 persons, 289 persons were excluded due to RA diagnoses registered in the Danish National Patient Registry at or prior to baseline and 1,149 persons due to missing data. Thus, a total of 55,037 participants (26,317 men and 28,720 women) with complete data and no previous RA diagnosis in the Danish National Patient Registry were included into our cohort study.

The median (IQR) duration of follow-up was 20.1 (19.5-20.9) years. During 1,023,558 person-years of follow-up, 666 individuals (210 men and 456 women) developed RA. The median (IQR) time to onset of RA was 10.8 years (6.1-15.6) and the median (IQR) age at RA onset was 68.0 (62.7-74.0) years for men and 67.8 (62.1-72.2) years for women. Table 1 shows the baseline characteristics of the total cohort and RA cases by gender.
At baseline, no major differences in anthropometric measures were found between the total cohort and cases, except that female RA cases were more likely to be overweight and obese, than the female cohort (54% vs. 49%, respectively). In both genders, more smokers were found among RA cases (Table 1).

Table 2 shows the sex-specific hazard ratios (HR) for the associations between anthropometric measures and overall incident RA. In women, higher fat percentage was associated with a higher risk of developing RA (HR 1.10 per 5% increment; 95% CI 1.02-1.18). Further, positive associations were also seen for higher WC (HR 1.05 per 5cm

increment; 95% CI 1.01-1.10), abdominal obesity (HR 1.18; 95% CI 0.96-1.45) compared to non-abdominal obesity, and BMI-defined obesity (HR 1.46; 95% CI 1.12-1.90) compared to normal weight. In men, there was no clear association between the anthropometric measures and the development of overall RA.

Post hoc sensitivity analyses were performed, using additional criteria in determining RA cases - patients with their first RA diagnosis in the Danish National Patient Registry after the enrolment into the Danish Diet, Cancer and Health cohort, who had subsequently, at least once, redeemed a prescription for a sDMARD and who had no ICD code for psoriatic or enteropathic arthropathies (ICD-8: 696.0; ICD-10: M07), systemic connective tissue disorders (ICD-8: 446, 716, 734; ICD-10: M30-M35), inflammatory bowel diseases (ICD-8: 563; ICD-10: K50-K51) or sarcoidosis (ICD-8: 135.99; ICD-10: D86) in the previous or following years in the Danish National Patient Registry. Excluding these diagnoses did not alter the results substantially (Supplementary Table 1). Furthermore, post hoc subanalyses stratifying by smoking status (current and never) were performed. The positive associations between BMI, WC, fat percentage and the risk of developing RA were maintained in both groups (Supplementary Table 2 and 3).

The results for the sero-positive RA patients are presented in Table 3. In both genders there was no clear association between the anthropometric measures and the development of sero-positive RA.

Table 4 shows the associations between each exposure of interest and the development of 'other RA'. In women, higher fat percentage was associated with a higher risk of other RA (HR 1.14 per 5% increment; 95% CI 1.04-1.25). Positive associations were also seen for

higher WC (HR 1.08 per 5cm increment; 95% CI 1.03-1.13), abdominal obesity (HR 1.30; 95% CI 1.00-1.70), overweight (HR 1.38; 95% CI 1.05-1.80) and obesity (HR 1.74; 95% CI 1.25-2.43). Among men, there was no association between fat percentage, WC or BMI and the development of 'other RA'.

Additional adjustment for potential confounders including alcohol consumption, educational level, physical activity and total intake of n-3 fatty acids did not change the results substantially (Tables 2-4).

Spline graphs of dose-response associations between the anthropometric measures and overall RA, sero-positive RA and 'other RA' risk in men and women can be found in Figure 1 and 2 and Supplementary Figures 1 and 2. There was a clear positive association between BMI, WC, fat percentage and the risk of developing ´overall RA´ and ´other RA´ in women. There was a weak positive association between high values of anthropometric measurements and the risk of developing ´overall RA´, ´sero-positive RA´ and ´other RA´ in men and ´sero-positive RA` in women.

To analyze the relationship between BMI and bioelectrical impedance-derived body fat percentage, the Pearsons' correlation coefficient (*r*) was calculated. There was a strong correlation between BMI and body fat percentage both in men ($r=0.88$, $p<0.001$) and in women ($r=0.91$, $p<0.001$). Scatter plots of the associations can be found in Supplementary Figure 3.

DISCUSSION

In this large population-based prospective cohort study, we observed that having higher body fat percentage, higher WC, being overweight (BMI 25-29.99 kg/m^2) or obese (BMI≥30 kg/m^2) was associated with a higher risk of ´overall RA´ and 'other RA' risk in women. We

found that overall RA risk was 10% higher for each 5% increment of total body fat in women. Women with a high WC were more likely to develop RA, than those with a low WC (5% higher risk for each 5cm increment of WC). Furthermore, obese women had nearly 50% higher risk of developing RA, than women with a normal BMI. We found weak positive associations between high values of the anthropometric measures and the development of RA in men and ´sero-positive RA` in women.

We found no previous studies exploring associations between bioimpedance-derived fat percentage, WC and RA risk. Our findings are in line with most of the previous studies investigating the associations between BMI and RA risk (11,12,15,19–22). We have, however, abstained from categorizing RA into sero-positive and sero-negative RA as it is well-known, that some sero-negative RA patients become sero-positive during the disease course (32). Further, some sero-negative patients may be misclassified as having RA, i.e. some of these patients might be obese and have osteoarthritis (48), psoriatic arthritis, polyarticular gout or fibromyalgia. Furthermore, proinflammatory activity in fat tissue and concomitant joint pain, as a part of osteoarthritis or fibromyalgia, may have led to the diagnosis of inflammatory arthritis. Therefore, in our study, we have defined three RA groups: overall RA, sero-positive RA and other RA.

The majority of studies, investigating the associations between BMI and the risk of serological subsets of RA, found obesity to be associated with the development of sero-negative RA (15,19,20,22). Only one study based on the Nurses' Health Study found obesity to be positively associated with sero-positive RA, and only among women diagnosed at age 55 years or younger (20). A large UK population-based prospective cohort study, the EPIC-Norfolk study, observed a nearly threefold higher risk of sero-negative (baseline RF and

ACPA negative) inflammatory polyarthritis in persons with obesity compared to normal weight persons (22). Two Scandinavian case-control studies yielded similar results (15,19). An association between obesity and the development of sero-negative RA was, however, not found in an American case-control study, which included 813 newly diagnosed RA patients (17). Two Swedish nested case-control studies, based on the Malmo Diet Cancer Study and the Malmo Preventive Medicine Project were also unable to establish this association (23). The inconsistency in the results could be explained by methodological differences between the studies, including data collection, a low number of sero-negative RA cases and possible misclassification of RA, especially sero-negative RA. The gender differences in our findings are similar to those of the Swedish case-control study (19). The findings might be explained by a different hormonal activity in men and women (49) or even by different pain responses (50) and hereby potential higher risk for RA misclassification in women.

The strengths of our study include the population-based prospective cohort study design with 20 years follow-up period and a large number of outcomes. The study included validated and detailed information on multiple body composition measures and covariates. Anthropometric measurements were obtained by a trained laboratory technician in a standardized manner, ensuring the reliability of the estimates (40). Detailed information on a range of already established and potential confounding factors was available for the study. However, adjusting for potential confounding factors in the analysis had only minor impact on the estimated hazard ratios. Only a minor number of participants in the Danish Diet, Cancer and Health cohort had missing data on any of exposure or any of the co-variates and

therefore they were not included in our study, allowing us to conduct the complete-case analysis.

Further, the Danish health system, is an uniformly organized, non-profit system, having near complete follow-up and enabling data linkage between population-based registries on the individual level.

We acknowledge the limitations of our study. Our study population consists only of Caucasian persons, the results may not be generalizable to other populations. Non-response to participate in the Danish Diet, Cancer and Health cohort could potentially have been related to the exposure, but not to the outcome (RA) because of the prospective study design. Virtually no loss to follow-up limits the possibility of response bias. Another limitation is the relatively low numbers of RA cases in men and ´sero-positive RA´ in women. It might be due to the age limit in our cohort and use of data from an administrative database. We might be underpowered to detect a true association in these groups due to the low numbers of events. Furthermore, in our study we used the baseline anthropometric measurements. Changes in body fat over time might have a different effect on the RA risk, which we were not able to analyze. Finally, as a consequence of the age limit in our cohort, we were unable to investigate the potential association of body composition and RA risk in persons younger than 50 years.

The association results between different anthropometric measurements and the risk of RA are consistent, reflecting the strong correlation between BMI and bioelectrical impedance-derived body fat percentage. Thus, in our study, BMI seems to be an adequate surrogate measure for body fat percentage.

In conclusion, a higher body fat percentage, higher waist circumference and obesity were associated with a higher risk of ´overall RA´ and ´other RA´ in women, indicating that excess total body fat volume per se rather than abdominal obesity is associated with RA risk. It remains unknown whether the association of the development of RA with excess adipose tissue simply reflects the presence of inflammatory activity as a part of the metabolic syndrome or whether it contributes to the development of autoimmune inflammatory joint disease.

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AUTHOR CONTRIBUTIONS

KO, KS, AT, AL contributed to the conception and design of the study. AL conducted the systemic review. KO, AL were involved in the acquisition of data. All authors contributed substantially to the analysis, interpretation of the results and manuscript drafting, revising it critically for intellectual content and approved the final version of the manuscript.

APPROVALS

The study was approved by the Danish Data Protection Agency (Jr. nr. 2012-41-0454). Data were treated in accordance with the law of personal data treatment (Law 429 of 31/05/2000). The study did not involve contact with patients or an intervention, therefore permission from the Danish Scientific Ethical Committee was not required.

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Table 1. Baseline demographic, anthropometric and lifestyle characteristics of all participants in the Danish Diet, Cancer and Health cohort and of those who developed RA, by gender

	Men		Women	
	Cohort (n=26,317)	**RA cases (n=210)**	**Cohort (n=28,720)**	**RA cases (n=456)**
Age, years	56 (53-60)	57 (53-61)	56 (53-61)	57 (53-61)
Height, cm	177 (172-181)	176 (172-180)	164 (160-168)	165 (161-169)
Weight, kg	82 (75-90)	82 (74-89)	67 (61-75)	69 (61-77)
BMI, kg/m^2	26 (24-29)	26 (24-29)	25 (23-28)	25 (23-28)
BMI grouped according to WHO				
Underweight, % (<18.5 kg/m^2)	0	0	1	1
Normal weight, % (18.5-24.9 kg/m^2)	34	37	50	45
Overweight, % (25-29.9 kg/m^2)	50	47	35	37
Obese, % (≥ 30 kg/m^2)	16	16	14	17
Waist circumference, cm	95 (89-102)	95 (88-101)	80 (74-88)	81 (75-90)
Abdominal obesity*				
Yes, %	23	24	25	27
No, %	77	76	75	73
Fat percentage	27 (23-30)	27 (23-30)	35 (30-39)	36 (31-40)
Educational level				
Primary school, %	10	10	19	22
Higher education, 1-2 years, %	14	15	32	35
Higher education, 3-4 years, %	42	43	38	34
Higher education, >4 years, %	34	32	11	9
Smoking status				

Never smoker, %	26	20	44	32
Former smoker, %	34	34	23	23
Current smoker, %	40	46	33	45
Total tobacco consumption for current smokers				
<15 g per day, %	27	25	47	48
15-25 g per day, %	49	54	49	49
>25 g per day, %	24	21	4	3
Alcohol, g per day	19 (11-40)	19 (8-37)	9 (3-17)	9 (3-18)
MET score, hours/week	54 (35-83)	57 (37-89)	59 (39-87)	55 (36-84)
Total intake of n-3 fatty acids, g/d	2.8 (2.2-3.6)	2.8 (2.2-3.6)	2.2 (1.7-2.8)	2.1 (1.7-2.7)

Medians (interquartile range) for continuous variables.

BMI – Body Mass Index, WHO – World Health Organization, WC – Waist Circumference, MET – Metabolic Equivalent of Task

* Abdominal obesity according to WHO recommended cut-off values: WC > 102 cm for men, WC > 88 cm for women.

Table 2. The relationship between anthropometric measures and the development of overall RA* by gender

	Cox proportional Hazard Ratio (95% confidence interval)			
	Overall RA* men (number of cases = 210)		Overall RA* women (number of cases = 456)	
	Age- and smoking-adjusted[1]	Multivariable-adjusted[2]	Age- and smoking-adjusted[1]	Multivariable-adjusted[2]
BMI, per 1-unit kg/m^2	1.01 (0.97–1.05)	1.01 (0.98–1.05)	1.03 (1.01–1.05)	1.03 (1.01–1.05)
BMI < 18.5 kg/m^2	N/A	N/A	0.59 (0.19–1.83)	0.58 (0.19–1.83)
BMI 18.5 – 24.99 kg/m^2	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
BMI 25 – 29.99 kg/m^2				
BMI ≥ 30 kg/m^2	0.87 (0.64–1.17)	0.87 (0.65–1.18)	1.22 (1.00–1.50)	1.20 (0.98–1.48)
	1.01 (0.67–1.53)	1.04 (0.69–1.57)	1.46 (1.12–1.90)	1.40 (1.08–1.83)
WC, per 5 cm increment	1.02 (0.95–1.09)	1.03 (0.96–1.10)	1.05 (1.01–1.10)	1.05 (1.01–1.09)
Abdominal obesity[3]				
No	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	1.15 (0.84-1.57)	1.18 (0.86–1.63)	1.18 (0.96-1.45)	1.15 (0.93-1.42)
Fat percentage, per 5% increment	1.02 (0.90–1.16)	1.03 (0.90–1.17)	1.10 (1.02–1.18)	1.08 (1.01–1.16)

*Patients, who were registered with one of ICD-10 "M05" or "M06" diagnostic codes at their first registration in the Danish National Patient Registry

BMI – Body Mass Index, WC – Waist Circumference

[1]Adjusted for age and smoking (status, duration, tobacco g/day)

[2]Adjusted for age, smoking (status, duration, tobacco g/day), socio-economic status (education level), alcohol consumption (g/day), physical activity (Metabolic Equivalent of Task, hours/week) and total intake of n-3 fatty acids (g/day)

[3]Abdominal obesity according to WHO recommended cut-off values: WC > 102 cm for men, WC > 88 cm for women

Table 3. The relationship between anthropometric measures and the development of sero-positive RA*, by gender

	Cox proportional Hazard Ratio (95% confidence interval)			
	Seropositive RA* men (number of cases = 79)		Seropositive RA* women (number of cases = 187)	
	Age- and smoking-adjusted[1]	Multivariable-adjusted[2]	Age- and smoking-adjusted[1]	Multivariable-adjusted[2]
BMI, per 1-unit kg/m^2	1.01 (0.95–1.08)	1.02 (0.96–1.10)	1.01 (0.97–1.04)	1.00 (0.97–1.04)
BMI < 18.5 kg/m^2	N/A	N/A	0.85 (0.21–3.47)	0.83 (0.20–3.38)
BMI 18.5 – 24.99 kg/m^2	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
BMI 25 – 29.99 kg/m^2				
BMI ≥ 30 kg/m^2	0.94 (0.57–1.53)	0.98 (0.60–1.61)	1.04 (0.75–1.42)	1.01 (0.73–1.39)
	1.00 (0.51-1.98)	1.12 (0.56–2.22)	1.12 (0.73–1.73)	1.04 (0.68–1.61)
WC, per 5 cm increment	1.02 (0.91–1.14)	1.05 (0.93–1.17)	1.01 (0.95–1.08)	1.01 (0.94–1.07)
Abdominal obesity[3]				
No	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	0.89 (0.51–1.54)	0.97 (0.56–1.69)	1.01 (0.73–1.42)	0.98 (0.70–1.37)
Fat percentage, per 5% increment	1.04 (0.84–1.29)	1.08 (0.88–1.34)	1.03 (0.93–1.15)	1.01 (0.91–1.13)

*Patients, who were registered with one of ICD-10 "M05" diagnostic codes at their first registration in the Danish National Patient Registry

BMI – Body Mass Index, WC – Waist Circumference

[1]Adjusted for age and smoking (status, duration, tobacco g/day)

[2]Adjusted for age, smoking (status, duration, tobacco g/day), socio-economic status (education level), alcohol consumption (g/day), physical activity (Metabolic Equivalent of Task, hours/week) and total intake of n-3 fatty acids (g/day)

[3]Abdominal obesity according to WHO recommended cut-off values: WC > 102 cm for men, WC > 88 cm for women

Table 4. The relationship between anthropometric measures and the development of other RA* by gender

	Cox proportional Hazard Ratio (95% confidence interval)			
	Other RA* men (number of cases = 131)		Other RA* women (number of cases = 269)	
	Age- and smoking-adjusted[1]	Multivariable-adjusted[2]	Age- and smoking-adjusted[1]	Multivariable-adjusted[2]
BMI, per 1-unit kg/m^2	1.01 (0.96–1.06)	1.01 (0.96–1.06)	1.04 (1.02–1.07)	1.04 (1.0–1.07)
BMI < 18.5 kg/m^2	N/A	N/A	0.36 (0.05–2.57)	0.36 (0.05–2.60)
BMI 18.5 – 24.99 kg/m^2	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
BMI 25 – 29.99 kg/m^2	0.83 (0.57–1.20)	0.81 (0.56–1.19)	1.38 (1.05–1.80)	1.37 (1.05–1.79)
BMI ≥ 30 kg/m^2	1.02 (0.61–1.71)	1.00 (0.59–1.67)	1.74 (1.25–2.43)	1.70 (1.22–2.39)
WC, per 5 cm increment	1.02 (0.93–1.11)	1.02 (0.93–1.11)	1.08 (1.03-1.13)	1.08 (1.02-1.13)
Abdominal obesity[3]				
No	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	1.32 (0.89–1.94)	1.31 (0.89–1.94)	1.30 (1.00–1.70)	1.28 (0.98–1.67)
Fat percentage, per 5% increment	1.00 (0.85–1.18)	1.00 (0.85–1.18)	1.14 (1.04–1.25)	1.13 (1.03–1.24)

*Patients, who were registered with one of ICD-10 "M06" diagnostic codes at their first registration in the Danish National Patient Registry

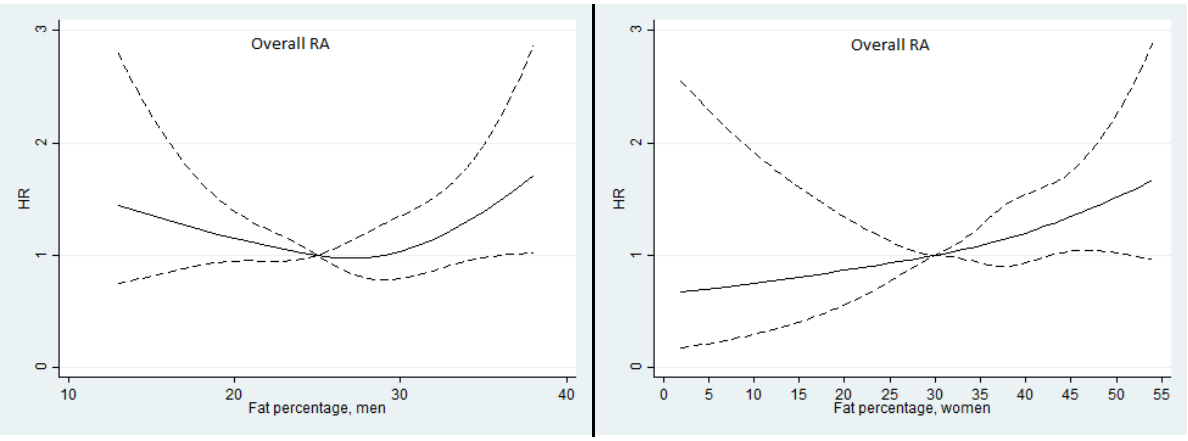
BMI – Body Mass Index, WC – Waist Circumference

[1]Adjusted for age and smoking (status, duration, tobacco g/day)

[2]Adjusted for age, smoking (status, duration, tobacco g/day), socio-economic status (education level), alcohol consumption (g/day), physical activity (Metabolic Equivalent of Task, hours/week) and total intake of n-3 fatty acids (g/day)

[3]Abdominal obesity according to WHO recommended cut-off values: WC > 102 cm for men, WC > 88 cm for women

Figure 1. Dose-response associations between body fat percentage and risk for development of overall[1] RA for persons enrolled in the Danish Diet, Cancer and Health cohort by gender. Four knots spline graphs, solid lines showing age and smoking adjusted (*) Cox proportional Hazard Ratio`s (HR) per 1% increment of total body fat and dash lines showing 95% confidence intervals.

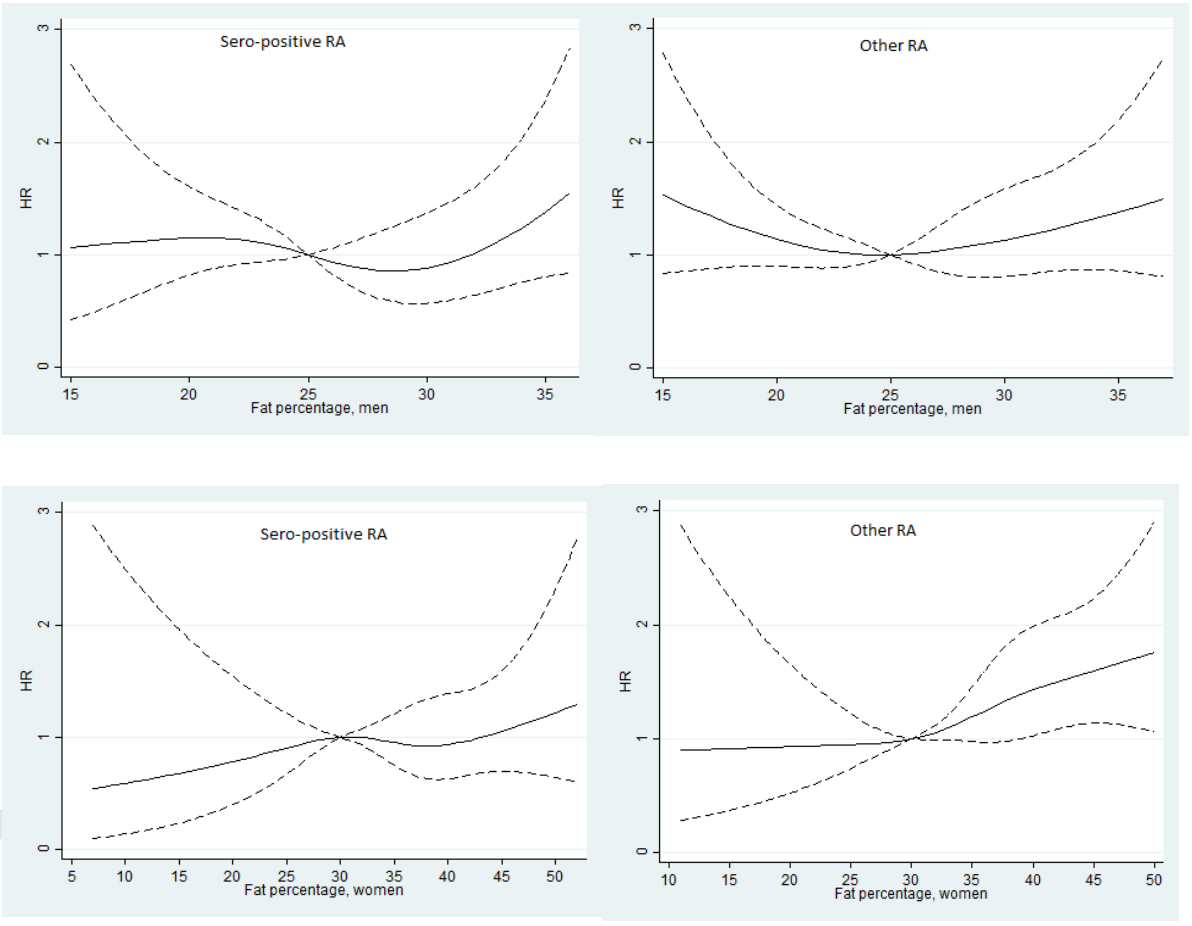


[1] Patients, who were registered with one of ICD-10 “M05” or “M06” diagnostic codes at their first registration in the Danish National Patient Registry

* Adjusted for age and smoking (status, duration, tobacco g/day).

RA – Rheumatoid Arthritis, ICD – International Classification of Diseases

Figure 2. Dose-response associations between body fat percentage and risk for development of sero-positive[1] RA and other[2] RA for persons enrolled in the Danish Diet, Cancer and Health cohort by gender. Four knots spline graphs, solid lines showing age and smoking adjusted (*) Cox proportional Hazard Ratio`s (HR) per 1% increment of total body fat and dash lines showing 95% confidence intervals.



[1] Patients, who were registered with one of ICD-10 “M05” diagnostic codes at their first registration in the Danish National Patient Registry

[2] Patients, who were registered with one of ICD-10 “M06” diagnostic codes at their first registration in the Danish National Patient Registry

* Adjusted for age and smoking (status, duration, tobacco g/day)

RA – Rheumatoid Arthritis, ICD – International Classification of Diseases