Abdominal Obesity in Comparison with General Obesity and Risk of Developing Rheumatoid Arthritis in Women

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ABSTRACT

Objective: Being overweight or obese increases rheumatoid arthritis (RA) risk among women, particularly among those diagnosed at younger age. Abdominal obesity may contribute to systemic inflammation more than general obesity, thus we investigated whether abdominal obesity, compared with general obesity, predicted RA risk in 2 prospective cohorts, the Nurses' Health Study (NHS) and NHS II.

Methods: We followed 50,682 women (1986-2014) in NHS and 47,597 women (1993-2015) in NHS II, without RA at baseline. Waist circumference (WC), body mass index (BMI), health outcomes and covariate data were collected through biennial questionnaires. Incident RA cases and serologic status were identified by chart review. We examined the associations of WC and BMI with RA risk using time-varying Cox proportional hazards models. We repeated analyses restricted to age ≤55 years.

Results: During 28 years of follow-up, we identified 844 incident RA cases (527 NHS, 317 NHS II). Women with WC >35 inches (88 cm) had increased RA risk (HR 1.22, 95% CI 1.06-1.41). A similar association was observed for seropositive RA, which was stronger among young and middle-aged women. Further adjustment for BMI attenuated the association to null. In contrast, BMI was associated with RA ($HR_{BMI \geq 30 vs < 25}$ 1.33, 95% CI 1.05-1.68) and seropositive RA, even after adjusting for WC, and, as in WC analyses, this association was stronger among young and middle-aged women.

Conclusion: Abdominal obesity was associated with increased RA risk, particularly for seropositive RA, among young and middle-aged women, however, it did not independently contribute to RA risk beyond general obesity.

INTRODUCTION

The association between RA and abdominal obesity, in comparison to general obesity, is not well understood. Body Mass Index (BMI) has been associated with RA in several studies (1-4), including work from our group demonstrating that BMI is strongly associated with seropositive RA among young and middle-aged women (1). Abdominal obesity assessed using waist circumference (WC) has been shown in some studies to be a better measure of visceral fat (5), known to contribute to systemic inflammation (6, 7) more than adipose tissues at other anatomic sites. BMI is associated with body fat and inflammation, but cannot provide indication of body composition (fat versus lean mass) (8), or fat mass distribution, and therefore may not adequately explain the amount of visceral, or abdominal fat. While overall and visceral fat both have active metabolic roles (8), visceral fat has a unique inflammatory profile (9) and thus may provide a link between increased adiposity and RA incidence independently of overall adiposity.

Increased WC has been associated with increased risk of several diseases including hypertension (10), diabetes (10), coronary heart disease (11), cancer (12, 13), and other inflammatory diseases (14). Previous studies of WC and RA risk have shown mixed results, reporting both increased risk of RA with increasing WC, and a null association (15, 16). However, studies were limited by having a small number of RA cases or case-control design. BMI has been studied in relation to RA risk (1), with a positive association having been found in many studies. Understanding whether abdominal adiposity is more predictive of RA risk than BMI, may aid in understanding the role of different types of adiposity on disease pathogenesis. Our aim was to determine the association of WC, in comparison to BMI, with RA risk, given the important role of abdominal obesity in systemic inflammation and the knowledge that inflammation can be present long before disease onset (17).

MATERIALS AND METHODS

Study Population

The NHS is a prospective study, established in 1976, that included 121,700 female nurses aged 30-55 years at baseline, living in 11 U.S. states. NHS II began in 1989, enrolling 116,429 female nurses aged 25-42 at baseline from 14 U.S. states. Participants provided health and lifestyle data on extensive biennial questionnaires (**Figure 1**). We studied 50,682 women in NHS followed since 1986 (aged 40-67 years) and 47,597 women in NHS II followed since 1993 (aged 29-48 years) who provided data on WC and BMI. We excluded women with any self-reported connective tissue disease (CTD), including prevalent RA cases, diagnosed before 1986 in NHS and 1993 in NHS II. All components of the study were approved by the Partners HealthCare Institutional Review Board (approval #2011P001730); study participants provided written informed consent.

General and abdominal obesity assessment

To determine general obesity, BMI was calculated as weight in kilograms (kg) divided by height in meters (m) squared. Height was collected in 1976 in NHS and in 1989 in NHS II; weight was collected biennially from baseline for both cohorts. BMI was categorized as: underweight and normal weight (<25 kg/m^2) (women with BMI <10 kg/m^2 were excluded from analyses), overweight (25-<30 kg/m^2), and obese (≥30 kg/m^2)(18). We also considered BMI in more categories, to better understand its association with RA: 10-<18.5, 18.5-<23, 23-<25, 25-<27.5, 27.5-<30, 30-<32.5, 32.5+ kg/m^2.

Information on WC was collected in 1986, 1996, and 2000 in NHS; and in 1993 and 2005 in NHS II. Women were asked to measure WC at navel level while standing in a relaxed position, to the nearest ¼ inch without estimation, and not while wearing bulky clothing. Weight and waist measurement accuracy were evaluated in a validation study, having trained technicians visit participants twice (19). The Pearson correlation between self-report and the average of technician measurements were 0.89 for WC and 0.97 for body weight (19). If women were pregnant when WC was measured, their previous response to the WC question was utilized when available (when not available, they were excluded from the study). Abdominal obesity was defined as WC >35 inches (88 cm) following World Health Organization and American Heart Association guidelines (20, 21). To better understand the association, we grouped WC into more categories: <27, 27-<29, 29-<31, 31-<33, 33-<35, 35-<37, 37+ inches.

RA Case Definition

Women with incident RA were identified using a 2-step process. Physician diagnosis of RA was asked on biennial questionnaires except in 1994 and 1998 in the NHS and 1995 in the NHS II. A validated CTD screening questionnaire was mailed to participants who self-reported a new physician diagnosis of RA (22). Medical records for these women were independently validated by two rheumatologists using 1987 American College of Rheumatology (ACR) classification criteria (23) or 2010 ACR/EULAR revised criteria (24). This date of clinical diagnosis was used as the date of incident RA. We collected data on rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA) testing from medical records to determine serostatus at the time of diagnosis, and classified women as seropositive (RF and/or ACPA positive) or seronegative (RF and ACPA negative).

Covariates

Participants' demographic, reproductive, clinical and behavioral factors have been collected with biennial questionnaires, including age, census tract median family income, smoking, age at menarche, menopausal status and postmenopausal hormone (PMH) use. A validated physical activity questionnaire (25) included inquiries about time spent engaged in several discretionary physical activities per week. Calculation methodology for a total estimate of physical activity in metabolic equivalents per week was published elsewhere (26). Overall dietary quality was measured by an Alternate Healthy Eating Index (AHEI) described in detail elsewhere (27). Baseline BMI ranged from 12 to 89 kg/m^2 in the NHS and 13 to 85 kg/m^2 in the NHS II; AHEI score ranged from14 (lowest quality) to 98 (highest quality) in the NHS and 14 to 96 in the NHS II; and physical activity ranged from 0.2 to 725 METs/week in the NHS and 0.2 to 550 METs/week in the NHS II.

Statistical Analyses

We calculated age-standardized descriptive statistics for women in NHS and NHS II cohorts by WC category (≤35 or >35 in.) to summarize study participant characteristics; frequencies were calculated for categorical variables, while mean and standard deviation were calculated for continuous variables.

Data from NHS and NHS II were combined prior to conducting analyses. Exposure information was collected comparably across cohorts and the resulting larger sample size provided increased power to better assess age-specific effects. We used Cox proportional hazards models to assess the association between time-varying WC and incident RA. The

proportional hazards assumption was valid, testing an interaction term between exposures and follow-up time. We calculated person-year of follow up from baseline questionnaire to either (i) date of RA, CTD self-report or RA diagnosis, (ii) death, (iii) loss to follow-up, or (iv) end of follow-up (June 1, 2014, NHS; June 1, 2015, NHS II), whichever occurred first. Univariate analyses were performed for covariates in unadjusted models. In multivariable analyses, we adjusted for time-varying covariates (significant in unadjusted models at $p<0.10$): age, cohort, smoking pack-years (0, 0-20, 20+ pack years), AHEI (quartiles), physical activity (quartiles of MET hours/week), and menopausal status and PMH use (premenopausal, and PMH never, current, or past use) (**Supplementary Tables 1-3**). We additionally adjusted our WC analyses for BMI (continuous) to determine if the association between WC and RA might be independent of BMI. In multivariable analyses for BMI, the same variables were considered to be associated with RA and BMI as in the WC analysis, however, we additionally adjusted for WC (continuous) to clarify the association between BMI and RA independent of WC. Potential interaction of abdominal obesity (WC) by general obesity (BMI) was assessed in a separate model. In sensitivity analyses, additional adjustment for census-tract household income, age at menarche, and breastfeeding duration did not change results.

Secondary analyses investigated the association of obesity with RA risk by serostatus. Consistent with our previous study using NHS cohorts (1), we performed stratified analyses by age, dichotomized at 55 years (28-30).

In addition, we developed separate models including more categories of WC and BMI. All statistical tests were 2-sided at a statistical significance level of 0.05, performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

At baseline, women with a higher WC (>35 inches) had a higher BMI, as expected, compared to women with a lower WC (≤35 inches). Additionally, in both cohorts, women with increased WC were older, had a lower diet quality, drank less alcohol, had a lower median family income, and participated in less discretionary physical activity, while more were postmenopausal and more experienced menarche at <12 years of age (**Table 1**).

WC and BMI were correlated (Pearson correlation coefficient = 0.72). The proportion of women in each cohort who had a higher WC and BMI was similar: 11.1% of women in NHS, 12.7% in NHSII were obese; 18.2% in NHS, 18.7% in NHSII had a WC>35 in.

During up to 28 years of follow-up (2,748,799 person-years) in NHS and NHS II, 844 women developed RA. A total of 527 (62%) had seropositive RA and 317 (38%) had seronegative RA. The median follow-up time from baseline to RA onset for cases, in the pooled cohort, was 9.3 years (range 4.2-15.3 years).

Waist Circumference and Rheumatoid Arthritis Risk

In the age-adjusted model, WC was positively associated with RA ($HR_{WC>35 vs \leq 35\ in.}$ 1.25, 95% CI 1.08-1.44). This association remained after adjusting for confounding variables (HR 1.22, 95% CI 1.06-1.41), but was attenuated and no longer statistically significant when BMI was included (HR 1.04, 95% CI 0.87-1.24) (**Table 2**). There was no significant interaction between WC and BMI ($P_{interaction}$=0.69).

When stratifying by serostatus, WC was again positively associated with seropositive RA in age-adjusted (HR 1.33, 95% CI 1.12-1.59) and multivariable-adjusted (HR 1.31, 95% CI 1.10-1.58) analyses; this association attenuated to null when BMI was added to the model (HR 1.14,

95% CI 0.91-1.42). There was no significant association between WC and seronegative RA in all models (**Table 2**).

When stratifying by age, younger women had a stronger association of WC with RA risk than older women ($P_{interaction}$=0.01). Among women ≤55 years of age, WC was positively associated with RA in age-adjusted (HR 1.68, 95% CI 1.30-2.17) and multivariable models (HR 1.60, 95% CI 1.23-2.08) but this attenuated when BMI was added to the model (HR 1.25, 95% CI 0.89-1.75). Among women >55 years of age there was no significant association between WC and RA in age-adjusted or multivariate models, with or without BMI included (**Table 2**).

Figure 2 depicts the trend of increasing RA risk with increasing WC. Compared to those with a lower WC, women with a higher WC were at significantly increased risk of incident RA and seropositive RA, particularly among those ≤55 years of age. When adjusted for BMI, these associations substantially attenuated to null. Associations generally were not statistically significant for seronegative RA, with wide confidence intervals due to a smaller number of cases in each category in this sub-group.

BMI and Rheumatoid Arthritis Risk

In contrast to WC, BMI was associated with all RA and seropositive RA risk, even after adjusting for WC. BMI was associated with all RA ($HR_{overweight}$ 1.31, 95% CI 1.12-1.53; HR_{obese} 1.41, 95% CI 1.18-1.68), seropositive RA ($HR_{overweight}$ 1.32, 95% CI 1.08-1.61; HR_{obese} 1.41, 95% CI 1.13-1.77), and seronegative RA ($HR_{overweight}$ 1.30, 95% CI 1.00-1.67; HR_{obese} 1.39, 95% CI 1.04-1.86) prior to adjusting for WC. These associations remained significant for all RA and seropositive RA after adjusting for WC, and were nearly significant for seronegative RA. Women who were overweight or obese had a higher risk of RA when compared to women with

BMI <25 kg/m^2 for all RA ($HR_{overweight}$ 1.28, 95% CI 1.08-1.52; HR_{obese} 1.33, 95% CI 1.05-1.68; P_{trend}=0.01), and seropositive RA ($HR_{overweight}$ 1.27, 95% CI 1.02-1.57; HR_{obese} 1.28, 95% CI 0.95-1.72) after adjusting for WC. This association was nearly significant for seronegative RA ($HR_{overweight}$ 1.31, 95% CI 0.99-1.73; HR_{obese} 1.42, 95% CI 0.97-2.08) after adjusting for WC. Risk of RA was higher for women diagnosed earlier in life; among women ≤55 years of age, obese women were at a higher risk of all RA (HR 1.90, 95% CI 1.26-2.86; P_{trend}=0.002) and seropositive RA (HR 2.03, 95% CI 1.23-3.37; P_{trend}=0.01), when compared to women with BMI <25 kg/m^2 after adjusting for WC (**Table 3**).

Figure 3 shows a consistently increasing risk of all RA and seropositive RA with increasing BMI after adjusting for WC, especially among women ≤55 years of age. A similar trend was observed for seronegative RA with borderline significance.

DISCUSSION

In this large prospective study, increased WC was associated with increased RA risk, particularly seropositive RA among young and middle-aged women. However, we did not find that WC was an independent predictor of RA after adjusting for BMI. BMI, however, remained a strong independent risk factor for RA after adjusting for WC, particularly among young and middle-aged women. Our findings may have both public health and clinical implications. Body fitness and weight control may prevent future development of RA, especially for women with a high risk of RA (smokers or first-degree relatives of RA patients). Further, it may not be necessary to take a patient's WC measurement, as BMI appears to be a sufficient, and indeed stronger, predictor of RA risk.

The literature on abdominal obesity as assessed by WC and RA risk is sparse, and findings are not in agreement. In the Danish Diet, Cancer and Health cohort (15), there was no association between WC and RA when comparing WC >35 to ≤35 inches for all RA (HR 1.15, 95% CI 0.93-1.42) or seropositive RA (HR 0.98, 95% CI 0.70-1.37) (15). This study was limited by a small number of RA cases (n=269). A Swedish nested case-control study with 557 RA cases and 1671 matched controls found an increased RA risk with increasing WC ($HR_{per\ cm}$ 1.02, 95% CI 1.01-1.04) (16), however, this association did not remain in analyses on women alone (16). Neither of these studies adjusted for BMI. Our study, with a longitudinal design, ≤28 years of follow-up, and larger number of cases than other studies, provides clearer evidence of the association between abdominal obesity and RA risk among women, who might have a different association than men.

Both abdominal and general obesity have been associated with diabetes, cardiovascular disease, and mortality (31). In some populations, WC was more strongly related than BMI to outcomes including hypertension (32) and coronary heart disease (33). Both BMI and WC have previously been reported to be associated with RA (1-4, 15, 16, 34), but the relative strengths of these associations have not previously been compared. We found that, although increased WC was a risk factor for RA, BMI was the stronger predictor and remained associated with RA after adjusting for WC, but not vice versa (**Table 3**).

Our previous study using NHS data has demonstrated that BMI is a risk factor for RA, particularly among women ≤55 years ($HR_{overweight}$ 1.45, 95% CI 1.03-2.04, HR_{obese} 1.65, 95% CI 1.34-2.05) (1). We did not adjust for WC in the model, and had a longer follow-up period. Despite these differences, our findings remain consistent.

We performed stratified analyses by age, dichotomized at 55, as previous research has revealed differences in several characteristics and disease progression between early and late-onset RA (28, 29). Compared to older women, the younger women (age ≤55 years) in our study had a lower BMI and participated in more physical activity; they ate a less healthy diet and consumed less alcohol, yet more were current smokers, and the proportion of women who were postmenopausal was much lower (results not shown). Generally, those with early-onset are more likely to be RF or ACPA positive (35), and *HLA–DRB1* (*HLA-SE*) (36) and *PTPN22* (37) gene carriers, all of which are associated with RA and increased disease severity (35, 37, 38), while those with late-onset may specifically experience greater joint erosion, joint narrowing, and increased functional limitations (28). For our study, understanding the relationships of abdominal obesity in early vs. late-onset RA was of interest, considering the common onset of sarcopenia in older age leading to body composition change (8). However, at older ages, WC was not a risk factor for RA independently of BMI in our study. Younger and middle-aged women, however, were at significantly increased risk for RA, and particularly seropositive RA, when they had a higher WC or BMI.

Strengths of our study include its large sample size, prospective design, repeated measures of exposures and covariates, and high follow-up rate. Our study also has potential limitations. Self-reported WC may be subject to measurement error, leading to an attenuation of results, though WC measurement has been validated in the NHS cohort (19) where women were provided uniform instructions with illustrations for obtaining WC. WC measurements have been highly correlated with those taken by technicians (8, 39). WC is also not only a measure of visceral but also subcutaneous fat, and while it is an imperfect measure, it is as good as, or perhaps even superior to, BMI as a superficial measure of abdominal obesity (5, 40-42). While

the binary cut-point for WC has been endorsed by governing bodies, dichotomization may dampen signals at tails. We explored this using more WC categories and found that including BMI attenuated associations across the spectrum of WC. While we treated WC and BMI as confounders of each other, they are correlated and may alternatively be classified as mediators or separate constructs measuring the same biologic system. Despite this correlation, which may have resulted in a loss of power to detect an association, adjusting for BMI in our WC analyses was a useful method to investigate if fat distribution (WC) was a predictor of RA risk independently of general obesity (BMI) (8). Other studies have used a similar approach, including both BMI and WC in the same regression model to conduct analyses investigating the independent contribution of these two measures of adiposity on risk of chronic diseases (10, 31). Next, it is possible that obese women may have been inappropriately diagnosed with RA rather than with other forms of arthritis or chronic pain conditions. However, all study participants are trained nurses and had multiple opportunities to report RA during the follow-up period. If they did report RA, medical records were reviewed by 2 independent rheumatologists following strict ACR criteria to ensure accuracy of diagnosis. Any participants with self-reported RA that was not confirmed, or those that reported other related connective tissue disease not classified as an RA case, were excluded from analyses. Therefore, our findings were less likely to be due to differential misclassification for RA cases.

Further, on the topic of possible misclassification of RA serostatus. Serostatus was determined at time of diagnosis in the NHS cohorts, where RF testing for cases was relied upon prior to the early 2000s, after which ACPA testing became more widely available. Different test assays might have been used in community clinical sites, which might have had different performance characteristics. About 62% of RA cases were seropositive, which is similar to

what has been reported in other RA studies (43-45). Seroconversion (initially testing seronegative and later testing seropositive) or seroreversion (the opposite of seroconversion) may have occurred after diagnosis, however, this is relatively uncommon, having been reported in <5% of patients in other research studies (46, 47). The determination of serostatus only at the time of RA diagnosis mirrors clinical care since this is not usually measured serially and has been used in many other clinical and research studies. This method of defining serostatus has also be successful in identifying several risk factors for RA subtypes, including smoking among those with seropositive RA (48), and menopause among those with seronegative RA (49). And, although we adjusted for some major factors associated with RA and WC, unmeasured confounding may still be present. In sub-group analyses, we may not have had sufficient power to detect a statistically significant association after including all relevant covariates, as can be noticed where confidence intervals were wider and less precise than in analyses of other outcomes. Beyond body adiposity, other unknown mechanisms may be associated with RA development. There might be genes associated with obesity and RA that establishes a propensity for both and provides a potential link between them (34, 50). Trends in confounder patterns, such as smoking and postmenopausal hormone use, might have differed between our two cohorts and over time, however, we adjusted for cohort in our analyses to address this. Lastly, because this study included only women, results may not be generalizable to men.

In conclusion, increased WC was associated with increased RA risk in our large cohort of women, but this measure of abdominal obesity did not confer additional risk above that posed by increased BMI, or general obesity, which remains as an important independent RA risk factor.

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REFERENCES

1. Lu B, Hiraki LT, Sparks JA, Malspeis S, Chen CY, Awosogba JA, et al. Being overweight or obese and risk of developing rheumatoid arthritis among women: A prospective cohort study. Ann Rheum Dis 2014;73:1914-22.

2. Pedersen M, Jacobsen S, Klarlund M, Pedersen BV, Wiik A, Wohlfahrt J, et al. Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides. Arthritis Res Ther 2006;8:R133.

3. Symmons DP, Bankhead CR, Harrison BJ, Brennan P, Barrett EM, Scott DG, et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: Results from a primary care-based incident case-control study in norfolk, england. Arthritis Rheum 1997;40:1955-61.

4. Uhlig T, Hagen KB, Kvien TK. Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. J Rheumatol 1999;26:47-54.

5. Camhi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL, et al. The relationship of waist circumference and bmi to visceral, subcutaneous, and total body fat: Sex and race differences. Obesity (Silver Spring) 2011;19:402-8.

6. Stepanikova I, Oates GR, Bateman LB. Does one size fit all? The role of body mass index and waist circumference in systemic inflammation in midlife by race and gender. Ethn Health 2017;22:169-83.

7. Thorand B, Baumert J, Doring A, Herder C, Kolb H, Rathmann W, et al. Sex differences in the relation of body composition to markers of inflammation. Atherosclerosis 2006;184:216-24.

8. Hu FB. Obesity epidemiology. Oxford ; New York: Oxford University Press; 2008.

9. Alvehus M, Buren J, Sjostrom M, Goedecke J, Olsson T. The human visceral fat depot has a unique inflammatory profile. Obesity 2010;18:879-83.

10. Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: Evidence in support of current national institutes of health guidelines. Arch Intern Med 2002;162:2074-9.

11. Flint AJ, Rexrode KM, Hu FB, Glynn RJ, Caspard H, Manson JE, et al. Body mass index, waist circumference, and risk of coronary heart disease: A prospective study among men and women. Obes Res Clin Pract 2010;4:e171-e81.

12. Song M, Hu FB, Spiegelman D, Chan AT, Wu K, Ogino S, et al. Long-term status and change of body fat distribution, and risk of colorectal cancer: A prospective cohort study. Int J Epidemiol 2016;45:871-83.

13. Lee KR, Hwang IC, Han KD, Jung J, Seo MH. Waist circumference and risk of breast cancer in korean women: A nationwide cohort study. Int J Cancer 2018;142:1554-9.

14. Von Behren J, Lipsett M, Horn-Ross PL, Delfino RJ, Gilliland F, McConnell R, et al. Obesity, waist size and prevalence of current asthma in the california teachers study cohort. Thorax 2009;64:889-93.

15. Linauskas A, Overvad K, Symmons D, Johansen MB, Stengaard-Pedersen K, de Thurah A. Body fat percentage, waist circumference and obesity as risk factors for rheumatoid arthritis - a danish cohort study. Arthritis Care Res (Hoboken) 2018.

16. Ljung L, Rantapaa-Dahlqvist S. Abdominal obesity, gender and the risk of rheumatoid arthritis - a nested case-control study. Arthritis Res Ther 2016;18:277.

17. Demoruelle MK, Deane KD, Holers VM. When and where does inflammation begin in rheumatoid arthritis? Curr Opin Rheumatol 2014;26:64-71.

18. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults--the evidence report. National institutes of health. Obes Res 1998;6 Suppl 2:51S-209S.

19. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466-73.

20. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr., Tudor-Locke C, et al. 2011 compendium of physical activities: A second update of codes and met values. Med Sci Sports Exerc 2011;43:1575-81.

21. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 acc/aha guideline on the primary prevention of cardiovascular disease. Circulation 2019:CIR0000000000000678.

22. Karlson EW, Sanchez-Guerrero J, Wright EA, Lew RA, Daltroy LH, Katz JN, et al. A connective tissue disease screening questionnaire for population studies. Ann Epidemiol 1995;5:297-302.

23. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The american rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.

24. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 rheumatoid arthritis classification criteria: An american college of rheumatology/european league against rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-8.

25. Wolf AM, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Corsano KA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol 1994;23:991-9.

26. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Jr., Montoye HJ, Sallis JF, et al. Compendium of physical activities: Classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71-80.

27. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 2012;142:1009-18.

28. Calvo-Alen J, Corrales A, Sanchez-Andrada S, Fernandez-Echevarria MA, Pena JL, Rodriguez-Valverde V. Outcome of late-onset rheumatoid arthritis. Clin Rheumatol 2005;24:485-9.

29. Camacho EM, Verstappen SM, Lunt M, Bunn DK, Symmons DP. Influence of age and sex on functional outcome over time in a cohort of patients with recent-onset inflammatory polyarthritis: Results from the norfolk arthritis register. Arthritis Care Res (Hoboken) 2011;63:1745-52.

30. Pease CT, Bhakta BB, Devlin J, Emery P. Does the age of onset of rheumatoid arthritis influence phenotype?: A prospective study of outcome and prognostic factors. Rheumatology (Oxford) 1999;38:228-34.

31. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. Am J Clin Nutr 2004;79:379-84.

32. Zhang M, Zhao Y, Wang G, Zhang H, Ren Y, Wang B, et al. Body mass index and waist circumference combined predicts obesity-related hypertension better than either alone in a rural chinese population. Sci Rep 2016;6:31935.

33. Lofgren I, Herron K, Zern T, West K, Patalay M, Shachter NS, et al. Waist circumference is a better predictor than body mass index of coronary heart disease risk in overweight premenopausal women. J Nutr 2004;134:1071-6.

34. Qin B, Yang M, Fu H, Ma N, Wei T, Tang Q, et al. Body mass index and the risk of rheumatoid arthritis: A systematic review and dose-response meta-analysis. Arthritis research & therapy 2015;17:86.

35. Innala L, Berglin E, Moller B, Ljung L, Smedby T, Sodergren A, et al. Age at onset determines severity and choice of treatment in early rheumatoid arthritis: A prospective study. Arthritis research & therapy 2014;16:R94.

36. Weyand CM, Hicok KC, Conn DL, Goronzy JJ. The influence of hla-drb1 genes on disease severity in rheumatoid arthritis. Ann Intern Med 1992;117:801-6.

37. Karlson EW, Chibnik LB, Cui J, Plenge RM, Glass RJ, Maher NE, et al. Associations between human leukocyte antigen, ptpn22, ctla4 genotypes and rheumatoid arthritis phenotypes of autoantibody status, age at diagnosis and erosions in a large cohort study. Annals of the rheumatic diseases 2008;67:358-63.

38. Berglin E, Johansson T, Sundin U, Jidell E, Wadell G, Hallmans G, et al. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by iga-rf at disease onset. Annals of the rheumatic diseases 2006;65:453-8.

39. Freudenheim JL, Darrow SL. Accuracy of self-measurement of body fat distribution by waist, hip, and thigh circumferences. Nutr Cancer 1991;15:179-86.

40. Pouliot MC, Despres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, et al. Waist circumference and abdominal sagittal diameter: Best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994;73:460-8.

41. Ross R, Leger L, Morris D, de Guise J, Guardo R. Quantification of adipose tissue by mri: Relationship with anthropometric variables. J Appl Physiol (1985) 1992;72:787-95.

42. van der Kooy K, Leenen R, Seidell JC, Deurenberg P, Visser M. Abdominal diameters as indicators of visceral fat: Comparison between magnetic resonance imaging and anthropometry. Br J Nutr 1993;70:47-58.

43. Huang S, He X, Doyle TJ, Zaccardelli A, Marshall AA, Friedlander HM, et al. Association of rheumatoid arthritis-related autoantibodies with pulmonary function test abnormalities in a rheumatoid arthritis registry. Clin Rheumatol 2019;38:3401-12.

44. Barra LJ, Pope JE, Hitchon C, Boire G, Schieir O, Lin D, et al. The effect of rheumatoid arthritis-associated autoantibodies on the incidence of cardiovascular events in a large inception cohort of early inflammatory arthritis. Rheumatology (Oxford) 2017;56:768-76.

45. Harrold LR, Litman HJ, Connolly SE, Kelly S, Hua W, Alemao E, et al. Effect of anticitrullinated protein antibody status on response to abatacept or antitumor necrosis factor-alpha therapy in patients with rheumatoid arthritis: A us national observational study. J Rheumatol 2018;45:32-9.

46. da Mota LM, Santos Neto LL, Pereira IA, Burlingame R, Menard HA, Laurindo IM. Autoantibodies in early rheumatoid arthritis: Brasilia cohort: Results of a three-year serial analysis. Rev Bras Reumatol 2011;51:564-71.

47. Hiwa R, Ohmura K, Nakabo S, Terao C, Murakami K, Nakashima R, et al. Only rheumatoid factor-positive subset of anti-citrullinated peptide/protein antibody-negative rheumatoid arthritis may seroconvert to anti-citrullinated peptide/protein antibody-positive. Int J Rheum Dis 2017;20:731-6.

48. Costenbader KH, Feskanich D, Mandl LA, Karlson EW. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. Am J Med 2006;119:503 e1-9.

49. Bengtsson C, Malspeis S, Orellana C, Sparks JA, Costenbader KH, Karlson EW. Association between menopausal factors and the risk of seronegative and seropositive rheumatoid arthritis: Results from the nurses' health studies. Arthritis Care Res (Hoboken) 2017;69:1676-84.

50. Crowson CS, Matteson EL, Davis JM, 3rd, Gabriel SE. Contribution of obesity to the rise in incidence of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2013;65:71-7.

TABLE 1. AGE-STANDARDIZED BASELINE CHARACTERISTICS IN NURSES' HEALTH STUDY (1986) AND NURSES' HEALTH STUDY II (1993)

Values are means (SD) for continuous variables; percentages for categorical variables, and are standardized to the age distribution of the study population.
[1]35 inches is equal to 88 cm. [2]Value is not age adjusted.

TABLE 2. HAZARD RATIOS (95% CI) FOR RHEUMATOID ARTHRITIS BY WAIST CIRCUMFERENCE (WC) IN NURSES' HEALTH STUDY (NHS, 1986-2014) AND NURSES' HEALTH STUDY II (NHS II, 1993-2015)

The cutpoint for WC was based on WHO and AHA recommendations.
[1]35 inches is equivalent to 89 cm. [2]Adjusted for age, cohort, smoking pack-years (0, 0-20, 20+ pack years), alternate healthy eating index (diet score quartiles), physical activity (quartiles of metabolic equivalent hours per week), and menopausal status and postmenopausal hormone use (premenopausal, PMH with never use, PMH with current use, and PMH past use). [3]Additionally adjusted for BMI (continuous).

TABLE 3. HAZARD RATIOS (95% CI) FOR RHEUMATOID ARTHRITIS BY BODY MASS INDEX (BMI) IN NURSES' HEALTH STUDY (NHS, 1986-2014) AND NURSES' HEALTH STUDY II (NHS II, 1993-2015), ADJUSTED FOR COVARIATES INCLUDING WAIST CIRCUMFERENCE

[1]Adjusted for age, cohort (NHS, NHS II), smoking pack-years (0, >0-20, 20+ pack years), alternate healthy eating index (diet score quartiles), physical activity (quartiles of metabolic equivalent hours per week), and menopausal status and postmenopausal hormone use (premenopausal, PMH with never use, PMH with current use, and PMH past use).
[2]Additionally adjusted for waist circumference (continuous).

FIGURE 1. QUESTIONNAIRE TIMELINE INCLUDING YEARS OF HEALTH STATUS QUESTIONNAIRES, WAIST CIRCUMFERENCE QUESTION, START OF FOLLOW-UP AND END OF FOLLOW-UP.

[1]Information about Rheumatoid Arthritis was asked in all years except 1994 and 1998 in NHS.
[2]Information about Rheumatoid Arthritis was asked in all years except 1995 in NHS II.

FIGURE 2. MULTIVARIABLE ADJUSTED HAZARD RATIOS (95% CI) FOR RHEUMATOID ARTHRITIS WITH INCREASING WAIST CIRCUMFERENCE (INCHES) IN NURSES' HEALTH STUDY (NHS, 1986-2014) AND NURSES' HEALTH STUDY II (NHS II, 1993-2015), WITH AND WITHOUT ADJUSTMENT FOR BODY MASS INDEX (BMI).

WC categories: <27, 27-<29 (reference), 29-<31, 31-<33, 33-<35, 35-<37, and 37+ inches. Adjusted for age, cohort, smoking pack-years (0, >0-20, 20+ pack years), alternate healthy eating index (diet score quartiles), physical activity (quartiles of metabolic equivalent hours per week), and menopausal status and postmenopausal hormone use (premenopausal, PMH with never use, PMH with current use, and PMH past use).

FIGURE 3. MULTIVARIABLE ADJUSTED HAZARD RATIOS (95% CI) FOR RHEUMATOID ARTHRITIS WITH INCREASING BODY MASS INDEX (BMI) IN NURSES' HEALTH STUDY (NHS, 1986-2014) AND NURSES' HEALTH STUDY II (NHS II, 1993-2015), ADJUSTED FOR COVARIATES INCLUDING WAIST CIRCUMFERENCE, FOR ALL AGES AND FOR THOSE DIAGNOSED AT AGE 55 OR EARLIER

BMI categories: 10-<18.5, 18.5-<23 (reference), 23-<25, 25-<27.5, 27.5-<30, 30-<32.5, and 32.5+ kg/m^2. Adjusted for age, cohort, waist circumference (continuous), smoking pack-years (0, >0-20, 20+ pack years), alternate healthy eating index (diet score quartiles), physical activity (quartiles of metabolic equivalent hours per week), and menopausal status and postmenopausal hormone use (premenopausal, PMH with never use, PMH with current use, and PMH past use).

	NHS		NHS II		Pooled	
	WC≤35 in.[1] (n=41,203)	**WC>35 in.** (n=9,078)	**WC≤35 in.** (n=38,089)	**WC>35 in.** (n=8,949)	**WC≤35 in.** (n=80172)	**WC>35 in.** (n=18096)
Age (years)[2]	53.2 (7.1)	55.2 (6.8)	40.5 (4.6)	41.6 (4.5)	47.1 (8.8)	48.5 (8.9)
Median family income ($1000)	65.3 (26.6)	60.3 (22.7)	63.4 (23.4)	57.7 (20.3)	64.4 (25.1)	58.9 (21.6)
BMI (kg/m^2)	23.3 (3.0)	30.9 (4.8)	22.7 (3.0)	31.9 (6.2)	23.0 (3.0)	31.4 (5.6)
Alternative Health Eating Index	50.8 (10.6)	48.2 (9.9)	49.4 (11.1)	46.9 (10.8)	50.1 (10.9)	47.7 (10.4)
Alcohol consumption (grams/day)	6.9 (10.4)	5.1 (10.4)	3.4 (6.3)	2.4 (6.0)	5.3 (9.0)	3.8 (8.6)
Physical activity (MET-hours/week)	15.8 (21.9)	10.6 (16.5)	23.1 (28.8)	16.0 (22.7)	19.2 (25.6)	13.4 (20.0)
Current smoker, %	21.1	17.5	11.0	11.7	16.3	14.4
Age at menarche <12 yrs, %	20.9	27.5	21.8	32.1	21.4	29.8
Parity (≥1 children), %	92.5	93.0	76.0	74.1	84.7	83.0
Breastfeeding duration (≥12 months), %	16.8	16.8	35.3	29.6	25.6	23.4
Postmenopausal, %	69.8	71.4	4.8	5.9	38.5	38.6
Postmenopausal hormone use, %	28.4	19.4	4.2	4.9	14.7	10.7

	All participants (all ages)		*Younger* (age ≤55 years)		*Older* (age >55 years)	
	WC ≤35 in.[1]	**WC >35 in.[1]**	**WC ≤35 in.[1]**	**WC >35 in.[1]**	**WC ≤35 in.[1]**	**WC >35 in.[1]**
All RA						
Cases	524	320	179	93	345	227
Person-years	1,851,988	896,811	782,846	231,878	1,129,680	711,767
Age-adjusted	1.00 (Ref)	**1.25 (1.08,1.44)**	1.00 (Ref)	**1.68 (1.30,2.17)**	1.00 (Ref)	1.10 (0.93,1.31)
Multivariable model 1[2]	1.00 (Ref)	**1.22 (1.06,1.41)**	1.00 (Ref)	**1.60 (1.23,2.08)**	1.00 (Ref)	1.09 (0.92,1.30)
Multivariable model 2[3]	1.00 (Ref)	1.04 (0.87,1.24)	1.00 (Ref)	1.25 (0.89,1.75)	1.00 (Ref)	0.98 (0.80,1.21)
Seropositive RA						
Cases	319	208	111	67	208	141
Person-years	1,849,494	895,626	781,592	231,491	1,128,417	710,945
Age-adjusted	1.00 (Ref)	**1.33 (1.12,1.59)**	1.00 (Ref)	**1.91 (1.40,2.61)**	1.00 (Ref)	1.13 (0.91,1.40)
Multivariable model 1[2]	1.00 (Ref)	**1.31 (1.10,1.58)**	1.00 (Ref)	**1.82 (1.32,2.49)**	1.00 (Ref)	1.13 (0.91,1.41)
Multivariable model 2[3]	1.00 (Ref)	1.14 (0.91,1.42)	1.00 (Ref)	1.37 (0.91,2.05)	1.00 (Ref)	1.07 (0.82,1.39)
Seronegative RA						
Cases	205	112	68	26	137	86
Person-years	1,847,701	894,949	780,688	231,100	1,127,515	710,643
Age-adjusted	1.00 (Ref)	1.11 (0.88,1.41)	1.00 (Ref)	1.29 (0.81,2.04)	1.00 (Ref)	1.06 (0.80,1.39)
Multivariable model 1[2]	1.00 (Ref)	1.08 (0.85,1.38)	1.00 (Ref)	1.22 (0.76,1.95)	1.00 (Ref)	1.03 (0.78,1.36)
Multivariable model 2[3]	1.00 (Ref)	0.89 (0.67,1.20)	1.00 (Ref)	1.03 (0.57,1.88)	1.00 (Ref)	0.86 (0.61,1.19)

	All participants (all ages)				*Younger participants* (age ≤55 years)			
	BMI<25	**25≤BMI<30**	**BMI ≥30**	**p trend**	**BMI<25**	**25≤BMI<30**	**BMI ≥30**	**p trend**
All RA								
Cases Person-years	359 1,098,232	286 555,478	199 494,402		120 576,527	76 258,613	76 179,585	
Multivariable model 1[1]	1.00 (Ref)	**1.31 (1.12,1.53)**	**1.41 (1.18,1.68)**	0.001	1.00 (Ref)	1.32 (0.99,1.78)	**1.88 (1.39,2.53)**	0.001
Multivariable model 2[2]	1.00 (Ref)	**1.28 (1.08,1.52)**	**1.33 (1.05,1.68)**	0.01	1.00 (Ref)	1.33 (0.97,1.82)	**1.90 (1.26,2.86)**	0.002
Seropositive RA								
Cases Person-years	223 1,404,501	179 818,695	125 521,923		73 575,616	52 258,166	53 179,300	
Multivariable model 1[1]	1.00 (Ref)	**1.32 (1.08,1.61)**	**1.41 (1.13,1.77)**	0.001	1.00 (Ref)	**1.47 (1.02,2.10)**	**2.13 (1.47,3.07)**	0.001
Multivariable model 2[2]	1.00 (Ref)	**1.27 (1.02,1.57)**	1.28 (0.95,1.72)	0.08	1.00 (Ref)	1.44 (0.98,2.12)	**2.03 (1.23,3.37)**	0.01
Seronegative								
Cases/Person years	136 1,403,393	107 817,865	74 521,391		47 575,130	24 257,719	23 178,965	
Multivariable model 1[1]	1.00 (Ref)	**1.30 (1.00,1.67)**	**1.39 (1.04,1.86)**	0.02	1.00 (Ref)	1.09 (0.66,1.79)	1.46 (0.87,2.45)	0.16
Multivariable model 2[2]	1.00 (Ref)	1.31 (0.99,1.73)	1.42 (0.97,2.08)	0.06	1.00 (Ref)	1.15 (0.67,1.97)	1.67 (0.82,3.40)	0.17

Figure 1

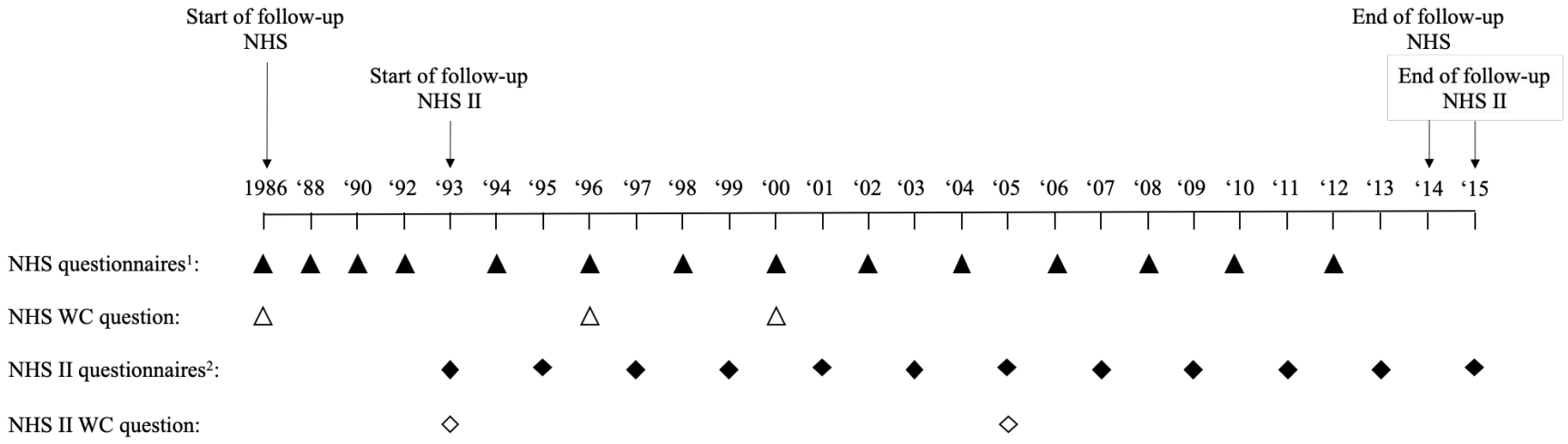

Figure 1.

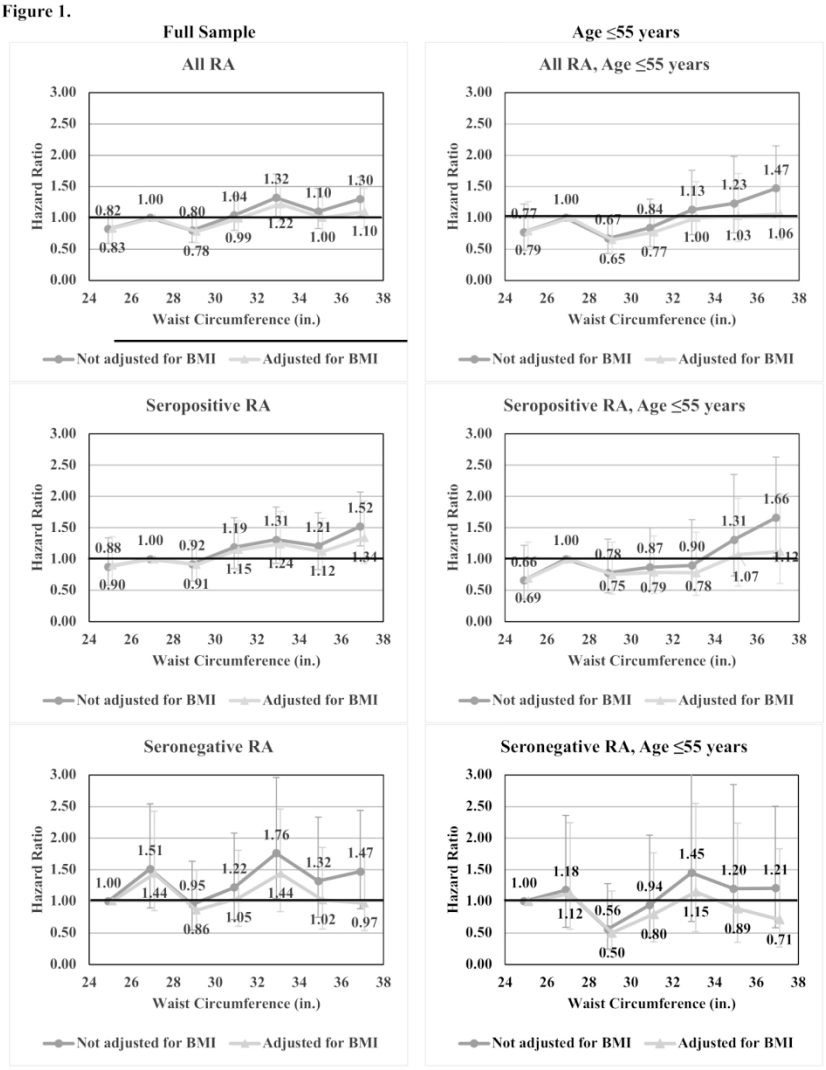

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FIGURE 2. MULTIVARIABLE ADJUSTED HAZARD RATIOS (95% CI) FOR RHEUMATOID ARTHRITIS WITH INCREASING WAIST CIRCUMFERENCE (INCHES) IN NURSES' HEALTH STUDY (NHS, 1986-2014) AND NURSES' HEALTH STUDY II (NHS II, 1993-2015), WITH AND WITHOUT ADJUSTMENT FOR BODY MASS INDEX (BMI).

WC categories: <27, 27-<29 (reference), 29-<31, 31-<33, 33-<35, 35-<37, and 37+ inches. Adjusted for age, cohort, smoking pack-years (0, >0-20, 20+ pack years), alternate healthy eating index (diet score quartiles), physical activity (quartiles of metabolic equivalent hours per week), and menopausal status and postmenopausal hormone use (premenopausal, PMH with never use, PMH with current use, and PMH past use).

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Figure 2.

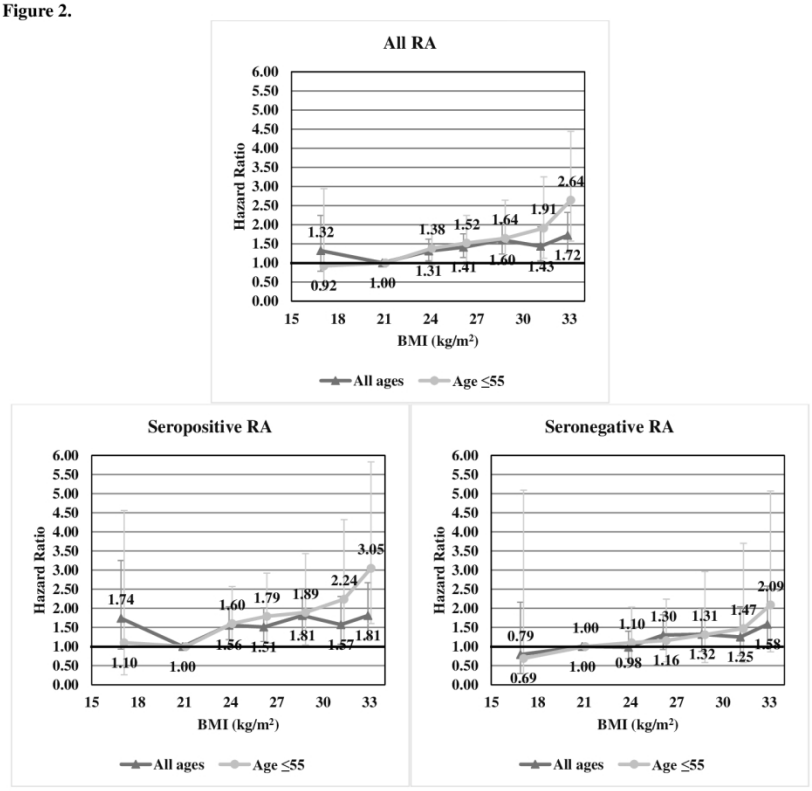

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FIGURE 3. MULTIVARIABLE ADJUSTED HAZARD RATIOS (95% CI) FOR RHEUMATOID ARTHRITIS WITH INCREASING BODY MASS INDEX (BMI) IN NURSES' HEALTH STUDY (NHS, 1986-2014) AND NURSES' HEALTH STUDY II (NHS II, 1993-2015), ADJUSTED FOR COVARIATES INCLUDING WAIST CIRCUMFERENCE, FOR ALL AGES AND FOR THOSE DIAGNOSED AT AGE 55 OR EARLIER

BMI categories: 10-<18.5, 18.5-<23 (reference), 23-<25, 25-<27.5, 27.5-<30, 30-<32.5, and 32.5+ kg/m2. Adjusted for age, cohort, waist circumference (continuous), smoking pack-years (0, >0-20, 20+ pack years), alternate healthy eating index (diet score quartiles), physical activity (quartiles of metabolic equivalent hours per week), and menopausal status and postmenopausal hormone use (premenopausal, PMH with never use, PMH with current use, and PMH past use).

215x279mm (200 x 200 DPI)