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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 a younger age. Abdominal obesity may contribute to systemic inflammation more than general obesity; thus, we investigated whether abdominal obesity, compared to 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), 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 > 88 cm (35 in) 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 ($HR_{BMI \geq 30 \text{ vs } < 25}$ 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.

Key Indexing Terms: abdominal obesity, general obesity, rheumatoid arthritis

The association between RA and abdominal obesity, in comparison to general obesity, is not well understood. BMI has been associated with RA in several studies[1,2,3,4], 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 it cannot provide indication of body composition (fat vs 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 a 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 US states. NHS II began in 1989, enrolling 116,429 female nurses aged 25–42

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years at baseline, living in 14 US 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 yrs), and 47,597 women in NHS II, followed since 1993 (aged 29–48 yrs), 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 to < 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 to < 18.5, 18.5 to < 23, 23 to < 25, 25 to < 27.5, 27.5 to < 30, 30 to < 32.5, and 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 6 mm (1/4 in) without estimation, and not while wearing bulky clothing. Weight and waist measurement accuracy were evaluated in a validation study, with trained technicians visiting 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, the women were excluded from the study). Abdominal obesity was defined as WC > 88 cm (35 in), following World Health Organization and American Heart Association guidelines[20,21]. To better understand the association, we grouped WC into more categories: < 69 cm (< 27 in), 69–74 cm (27 to < 29 in), 74–79 cm (29 to < 31 in), 79–84 cm (31 to < 33 in), 84–88 cm (33 to < 35 in), 88–94 cm (35 to < 37 in), and 94+ cm (37+ in).

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 2 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 anticitrullinated 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 were 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 (MET) 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 from 14 (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 0.2–550 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 (≤ 88 or > 88 cm) to summarize study participant characteristics; frequencies were calculated for categorical variables, while mean and SD 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 hazard 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-years of follow-up from baseline questionnaire to either (1) date of RA, CTD self-report, or RA diagnosis; (2) death; (3) loss to follow-up; or (4) end of follow-up (NHS: June 1, 2014; NHS II: June 1, 2015), 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-yrs), AHEI (quartiles), physical activity (quartiles of MET h/week), and menopausal status and PMH use (premenopausal, and PMH never, current, or past use; Supplementary Tables 1–3, available with the online version of this article). 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[28,29,30].

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).

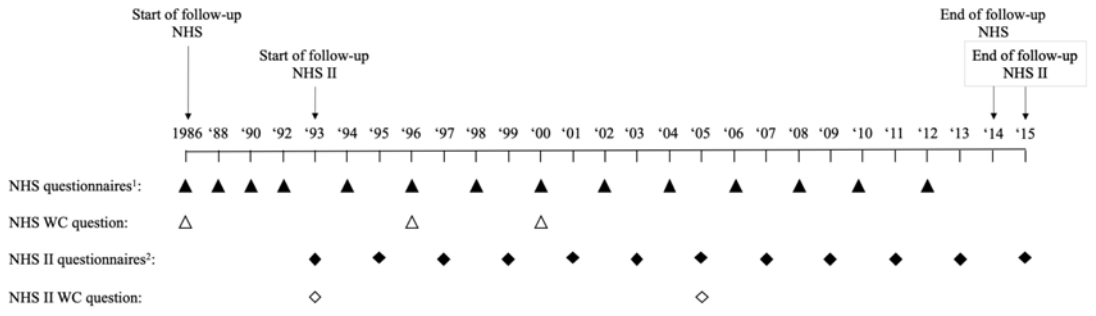

Figure 1. Questionnaire timeline including years of health status questionnaires, WC question, start of follow-up, and end of follow-up. [1] Information about RA was asked in all years except 1994 and 1998 in NHS. [2] Information about RA was asked in all years except 1995 in NHS II. NHS: Nurses' Health Study; RA: rheumatoid arthritis; WC: waist circumference.

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RESULTS

At baseline, women with a higher WC (> 88 cm) had a higher BMI, as expected, compared to women with a lower WC (≤ 88 cm). Additionally, in both cohorts, women with increased WC were older, had lower diet quality, drank less alcohol, had a lower median family income, and participated in less discretionary physical activity; more women were postmenopausal and more also 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 and 12.7% in NHS II were obese; 18.2% in NHS and 18.7% in NHS II had a WC > 88 cm (data not shown).

During up to 28 years of follow-up (2,748,799 person-yrs) in NHS and NHS II, 844 women developed RA. A total of 527 (62%) had seropositive RA, and 317 (38%) had seronegative RA (Table 2). 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 yrs).

WC and RA risk. In the age-adjusted model, WC was positively associated with RA ($HR_{WC>88vs\leq88cm}$ 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 ($P = 0.69$).

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 was 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 CI due to a smaller number of cases in each category in this subgroup.

BMI and RA 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/m² 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/m² after adjusting for WC (Table 3).

Table 1. Age-standardized baseline characteristics in Nurses' Health Study (NHS; 1986) and NHS II (1993).

	NHS		NHS II		Pooled	
	WC ≤ 88 cm[a], n = 41,203	WC > 88 cm[a], n = 9078	WC ≤ 88 cm[a], n = 38,089	WC 88 cm[a], n = 8949	WC ≤ 88 cm[a], n = 80,172	WC > 88 cm[a], n = 18,096
Age, yrs[b]	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, $000s	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/m²	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, g/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-h/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 mos), %	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

Values are means (SD) for continuous variables and percentages for categorical variables, and are standardized to the age distribution of the study population. [a]88 cm is equal to 35 inches. [b]Value is not age-adjusted. WC: waist circumference; MET: metabolic equivalence unit.

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Table 2. HR (95% CI) for RA by waist circumference (WC) in Nurses' Health Study (NHS; 1986–2014) and NHS II (1993–2015).

	All Participants, All Ages		Younger, ≤ 55 Yrs		Older, > 55 Yrs	
	WC ≤ 88 cm[a]	WC > 88 cm[a]	WC ≤ 88 cm[a]	WC > 88 cm[a]	WC ≤ 88 cm[a]	WC >88 cm[a]
All RA						
Cases	524	320	179	93	345	227
Person-yrs	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[b]	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[c]	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[b]	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[c]	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[b]	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[c]	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)

The cutpoint for WC was based on the World Health Organization and American Heart Assocation recommendations. Values in bold are statistically significant. [a]88 cm is equivalent to 35 inches. [b]Adjusted for age, cohort, smoking pack-years (0, 0–20, 20+ pack-yrs), Alternate Healthy Eating Index (diet score quartiles), physical activity (quartiles of metabolic equivalent h/week), and menopausal status and PMH use (premenopausal, PMH never use, PMH with current use, and PMH past use). [c]Additionally adjusted for BMI (continuous). PMH: postmenopausal hormone; RA: rheumatoid arthritis.

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 in 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 > 88 to ≤ 88 cm 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 a 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[1,2,3,4,15,16,34], 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 (aged ≤ 55 yrs) 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

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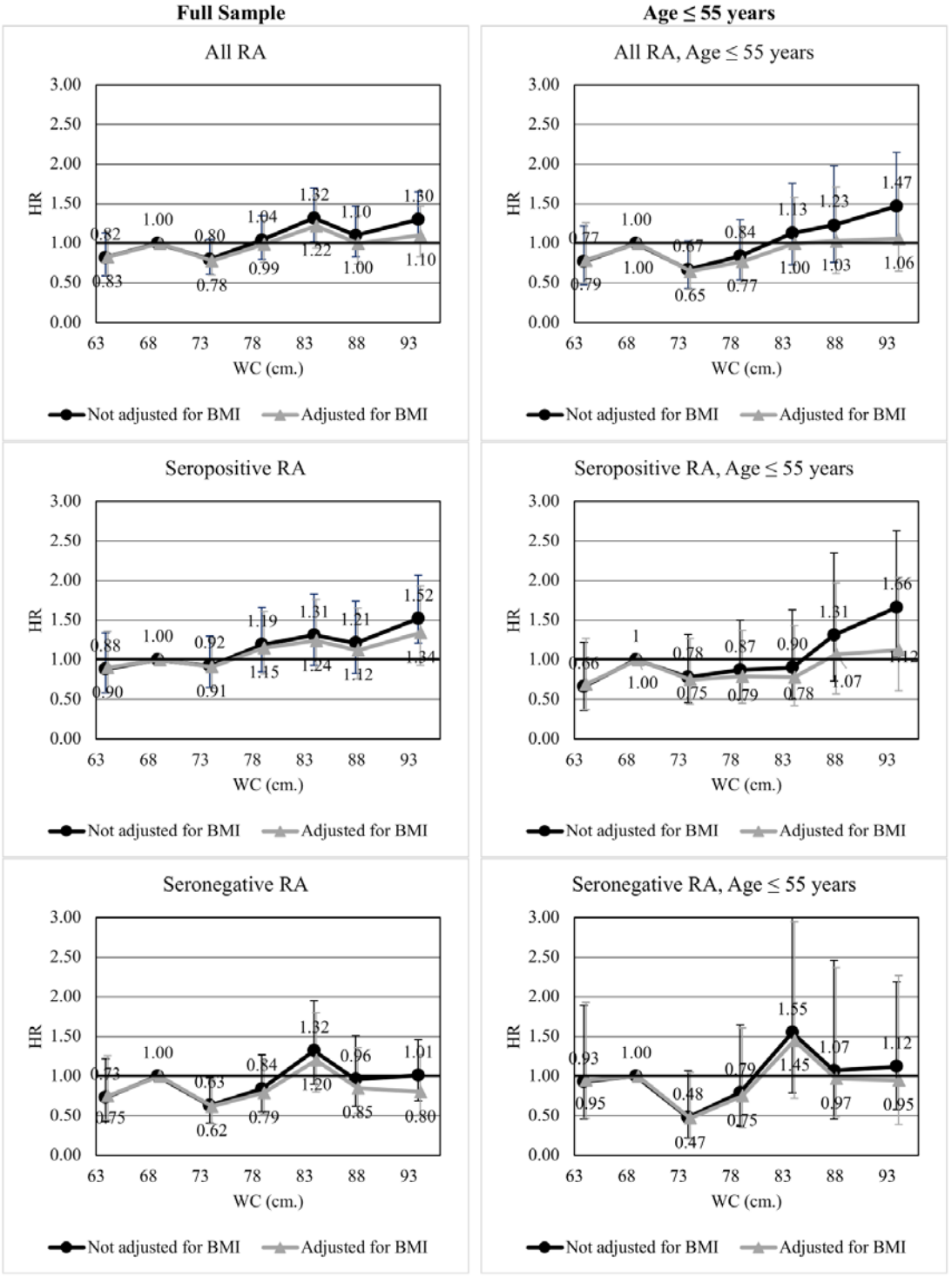

Figure 2. Multivariable adjusted HR (95% CI) for RA with increasing WC (inches) in the NHS (1986–2014) and NHS II (1993–2015), with and without adjustment for BMI. WC categories: < 69 cm (< 27 in), 69–74 cm (27 to < 29 in), 74–79 cm (29 to < 31 in), 79–84 cm (31 to < 33 in), 84–88 cm (33 to < 35 in), 88-94 cm (35 to < 37 in), and 94+ cm (37+ in). Adjusted for age, cohort, smoking pack-years (0, > 0 to 20, 20+ pack-yrs), Alternate Healthy Eating Index (diet score quartiles), physical activity (quartiles of MET h/week), and menopausal status and PMH use (premenopausal, PMH never use, PMH with current use, and PMH past use). MET: metabolic equivalent; NHS: Nurses' Health Study; PMH: postmenopausal hormone; RA: rheumatoid arthritis; WC: waist circumference.

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], whereas 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 versus late-onset

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Table 3. HR (95% CI) for rheumatoid arthritis by BMI in the Nurses' Health Study (NHS; 1986–2014) and NHSII (1993–2015).

	All Participants, All Ages				Younger participants, ≤ 55 Yrs			
	BMI < 25	25 ≤ BMI < 30	BMI ≥ 30	*P**	BMI < 25	25 ≤ BMI < 3	BMI ≥ 30	*P**
All RA								
Cases	359	286	199		120	76	76	
Person-yrs	1,098,232	555,478	494,402		576,527	258,613	179,585	
Multivariable model 1[a]	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[b]	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	223	179	125		73	52	53	
Person-yrs	1,404,501	818,695	521,923		575,616	258,166	179,300	
Multivariable model 1[a]	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[b]	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 RA								
Cases	136	107	74		47	24	23	
Person-yrs	1,403,393	817,865	521,391		575,130	257,719	178,965	
Multivariable model 1[a]	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[b]	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

Values in bold are statistically significant. [a]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 never use, PMH with current use, and PMH past use). [b] Additionally adjusted for waist circumference (continuous). * *P* values for trend. PMH: postmenopausal hormone; RA: rheumatoid arthritis.

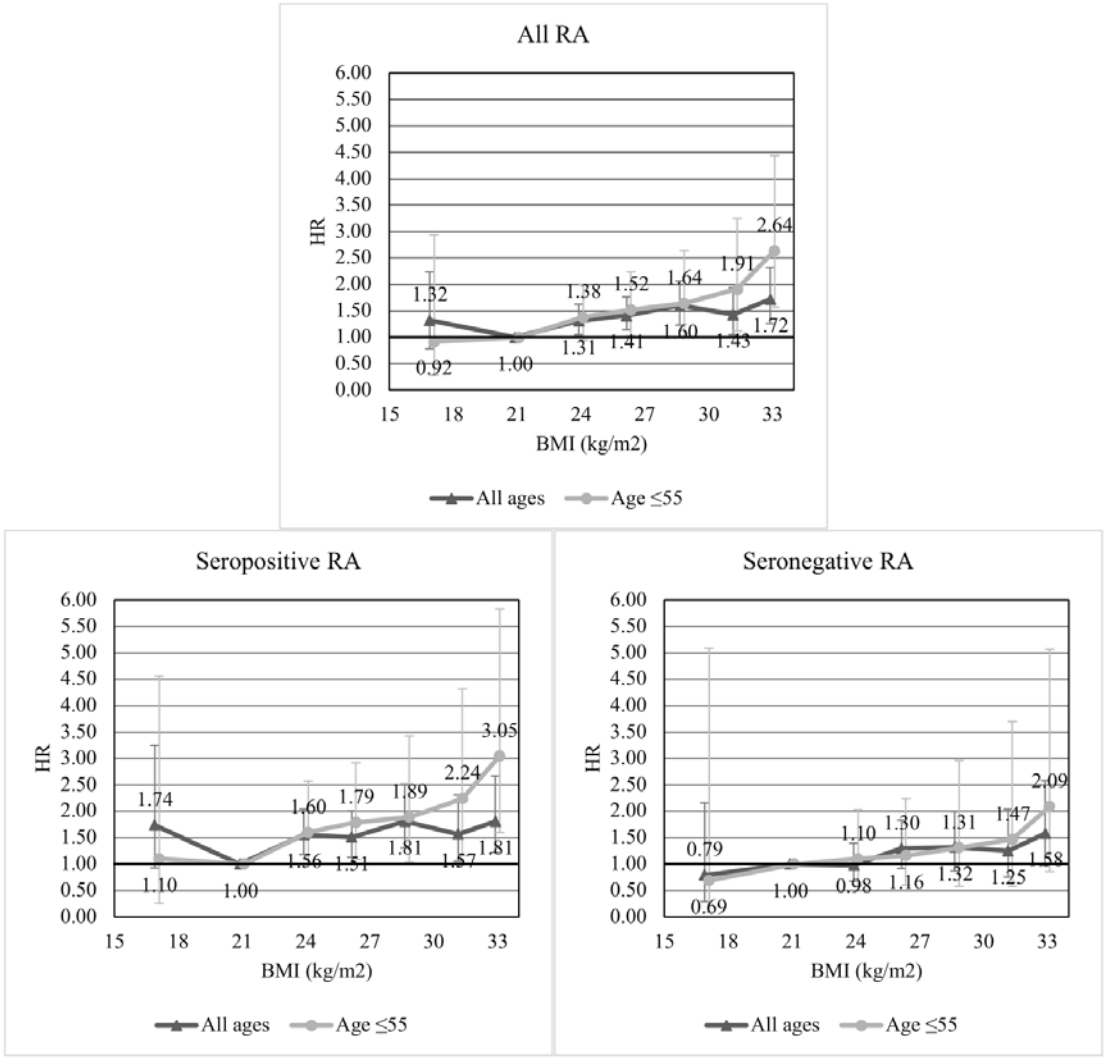

Figure 3. Multivariable adjusted HR (95% CI) for RA with increasing BMI in the NHS (1986–2014) and NHS II (1993–2015), adjusted for covariates including WC, for all ages and for those diagnosed at age 55 years or earlier. BMI categories: 10 to < 18.5, 18.5 to < 23 (reference), 23 to < 25, 25 to < 27.5, 27.5 to < 30, 30 to < 32.5, and 32.5+ kg/m^2. Adjusted for age, cohort, WC (continuous), smoking pack-years (0, > 0–20, 20+ pack-yrs), Alternate Healthy Eating Index (diet score quartiles), physical activity (quartiles of MET h/week), and menopausal status and PMH use (premenopausal, PMH never use, PMH with current use, and PMH past use). MET: metabolic equivalent; NHS: Nurses' Health Study; PMH: postmenopausal hormone; RA: rheumatoid arthritis; WC: waist circumference.

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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 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[5,40,41,42]. While the binary cutpoint 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 2 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 who reported other related CTD 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[43,44,45]. 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 been 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 subgroup analyses, we may not have had sufficient power to detect a statistically significant association after including all relevant covariates, as can be noticed where CI 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 establish a propensity for both and provide a potential link between them[34,50]. Trends in confounder patterns, such as smoking and postmenopausal hormone use, might have differed between our 2 cohorts and over time; however, we adjusted for cohort in our analyses to address this. Last, 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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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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