Original Article
EPIDEMIOLOGY/GENETICS

Obesity

High Population Attributable Fractions of Myocardial Infarction Associated with Waist–Hip Ratio

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Objective: To estimate population attributable fractions (PAF) of acute myocardial infarction (AMI) associated with anthropometric measures by sex and age.

Methods: The Cohort of Norway study identified 140,790 participants free of cardiovascular disease, 1994-2003. Participants were followed for AMI through 2009 by record linkages through the Cardiovascular Disease in Norway Project. PAFs were adjusted for age, smoking, systolic blood pressure, diabetes, and the ratio of total cholesterol to high-density lipoprotein cholesterol.

Results: The PAFs associated with a waist–hip ratio (WHR) in the top two quintiles were 26.1% (95% confidence interval, CI 14.6–36.1) for middle-aged women (<60 years, mean of 41 years) and 9.3% (95% CI 3.0–15.1) for similarly aged men after adjustment for body mass index (BMI) and conventional risk factors. However, PAFs associated with anthropometric measures in elderly participants (≥ 60 years, mean of 70 years) were nonsignificant in multivariable analyses. Also, WHR was a significant predictor of AMI among men and women without an enlarged waist circumference (<102 cm for men and < 88 cm for women) in adjusted analyses.

Conclusions: WHR measurements could improve identification of at-risk individuals above and beyond that of conventional risk factors, BMI, or an enlarged waist circumference.

Obesity (2016) **24**, 1162–1169. doi:10.1002/oby.21452

Introduction

Overweight and obesity are increasing in prevalence and considered a global public health concern affecting an estimated 1.9 billion adults 18 years of age and older worldwide in 2014 (1). The upward trend in weight status has consequences for increasing the chronic disease burden in populations (2-5). In the case-control INTERHEART study of 52 countries, the waist–hip ratio (WHR) showed a stronger relation with myocardial infarction than other commonly used anthropometric measures and had a population attributable risk over three times higher than that attributed to body mass index (BMI) (4). Aging, however, has been associated with a number of important body composition changes (6,7) which may modify the ability of anthropometric measures to predict coronary heart disease (CHD). In a comprehensive review of the implications of weight status among the elderly, the current World Health Organization (WHO) recommendations for optimal weight status and obesity thresholds were questioned for older adults (8). Based upon the Obesity Expert Panel systematic review, gaps in knowledge were recognized for potential age and sex differences in the implications of obesity measure cut points and the benefits of weight loss (9). Sex differences may exist where body composition measures may have different discriminatory capabilities in women compared to men. We, therefore, investigated whether there were age and sex differences in the prediction of acute myocardial infarction (AMI) by anthropometric measures in a large population-based prospective study in Norway.

Methods

Participants, aged 18 years or older, in the community-based regional health screenings of Cohort of Norway (CONOR), assembled 1994-2003 (10,11), formed the baseline of this prospective study. Of a total of 309,742 invitations for CONOR study participation, 59% (181,891) participated, of whom 173,243 men and women attended at least one health screening. Participants with a self-reported history of heart disease, stroke, angina, and current or past use of antihypertensive medications or with missing baseline health information ($n = 32,453$) were excluded, leaving a total of 140,790 participants for analyses. Only

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Funding agencies: The University of Bergen and the Norwegian Institute of Public Health.

Disclosure: The authors declared no conflict of interest.

Author contributions: GME and GST designed the research; GME, JI, GS, GEE, and SEV conducted analyses; GME wrote the manuscript; all authors contributed to interpretation of data and editing the manuscript and approved the final version submitted.

Additional Supporting Information may be found in the online version of this article.

Received: 12 August 2015; **Accepted:** 2 December 2015; **Published online 31 March 2016. doi:10.1002/oby.21452**

TABLE 1 Baseline demographic characteristics of CONOR participants free of cardiovascular disease at baseline, 1994-2003, by sex and age ($N = 140,790$)

	Men[a]		Women[a]	
	< 60 years ($n = 52,714$)	≥ 60 years ($n = 14,268$)	< 60 years ($n = 60,304$)	≥ 60 years ($n = 13,504$)
Age (years)	41.4 (9.0)	69.5 (6.3)	41.1 (9.1)	69.7 (7.1)
Systolic blood pressure (mm Hg)	132.1 (14.0)	145.9 (21.1)	123.2 (15.4)	148.0 (23.7)
Diastolic blood pressure (mm Hg)	77.6 (10.4)	83.4 (11.5)	72.6 (10.4)	79.8 (13.1)
Glucose (mmol/L)[b]	5.31 (1.26)	5.79 (1.75)	5.10 (1.02)	5.61 (1.58)
Total chol–HDL-C ratio	4.89 (1.59)	4.76 (1.49)	3.83 (1.27)	4.50 (1.48)
Enlarged waist (%)[c]	11.5	18.6	18.9	32.5
BMI (kg/m^2)				
Underweight (< 18.5)	0.4	0.8	1.5	1.6
Normal weight (18.5-24.9)	40.1	37.5	56.5	38.9
Overweight (25-29.9)	47.7	50.4	30.4	40.9
Obesity (≥ 30)	11.9	11.4	11.6	18.6
Waist–hip ratio	0.89 (0.06)	0.92 (0.06)	0.79 (10.6)	0.82 (0.06)
Self-reported diabetes (%)	1.0	3.8	0.9	3.2
Current daily smoking (%)	33.0	26.6	35.1	21.6
Any college education (%)	34.2	18.1	34.6	11.9

[a]Data presented as means (SD) unless noted as percent (%); all differences by age group for men and women are statistically significant ($P < 0.001$).
[b]Non-fasting values.
[c]≥102 cm for men and ≥88 cm for women.
chol, cholesterol; CONOR, Cohort of Norway; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation.

0.8% of individuals were lost to follow-up due to migration. Missing data for covariates were low for the majority of parameters (<1% for smoking, lipids, BMI, and blood pressure). However, waist circumference (WC) was missing for 17.4% of participants: 98.5% of the missing data were attributed to the lack of inclusion of this measure in one of the regional surveys (i.e., the 4th Tromsø Health Survey). The majority of the cohort is ethnic Norwegian.

Outcomes

A personal identifier, unique to each Norwegian resident, was used to identify status of CONOR participants as of December 31, 2009, through records linkages with the Norwegian Cause of Death Registry and national hospital discharge diagnoses data which were obtained through the Cardiovascular Disease in Norway Project (CVDNOR), 1994-2009 (12). The Regional Ethics Committee approved the baseline health surveys and follow-up record linkages. The outcome was hospitalization or death attributed to an AMI occurring during 1994-2009 using the International Classification of Diseases (ICD) codes (ICD-9 of 410; ICD-10 of I21 and I22).

Baseline risk factors

Body weight (kg) and height (cm) were measured with participants wearing light clothing without shoes. WC (cm) was measured at the umbilicus, or in people with obesity at the midpoint between the iliac crest and lower margin of ribs; hip circumference (cm) was measured at the maximum circumference around the buttocks. BMI (kg/m^2) and WHR (waist in cm/hip in cm) were calculated. Non-fasting total and high-density lipoprotein cholesterol (HDL-C) (mmol/L) were measured by an enzymatic method (Boehringer 148393. Boehringer-Mannheim, Federal Republic of Germany from 2000 Hitachi 917 auto analyze, Roche Diagnostic, Swizterland). The average of three systolic blood pressure readings taken by an automatic device (DINAMAP, Criticon, Tampa, FL) was used in analyses.

Statistical analyses

Age was first explored using three age groups: under 50, 50–69, and 70 years of age or older, in which stronger, intermediate, and weaker associations were observed between anthropometric measures and AMI risk from the youngest to oldest age groups, respectively (data not shown). To facilitate multivariable modeling and presentation of results, we used under 60 and 60 years of age or older as cutoff values for the analyses.

Descriptive statistics for baseline cohort characteristics are provided as means, standard deviations (SD), proportions, and Pearson's correlation coefficients (r). Cox survival analyses evaluated significance of interaction terms in the prediction of AMI. Given the significance of interaction terms (age by BMI, age by WHR, and sex by WHR), analyses were stratified by age and sex. The dose–response relationship between the continuous anthropometric measures and AMI was explored using restricted cubic spline functions with three knots using the median anthropometric measure as the reference value (13). Multiple Cox proportional hazards regression of AMI was conducted with results presented as hazard ratios (HR) and 95% confidence intervals (CI). The proportional hazards assumption was evaluated by Schoenfeld's test. The multivariable models considered conventional risk factors assessed at baseline: age (years), current daily smoking (yes versus no), systolic blood pressure (mm Hg), self-reported diabetes (yes versus no), and the total cholesterol–HDL-C ratio. WHR was

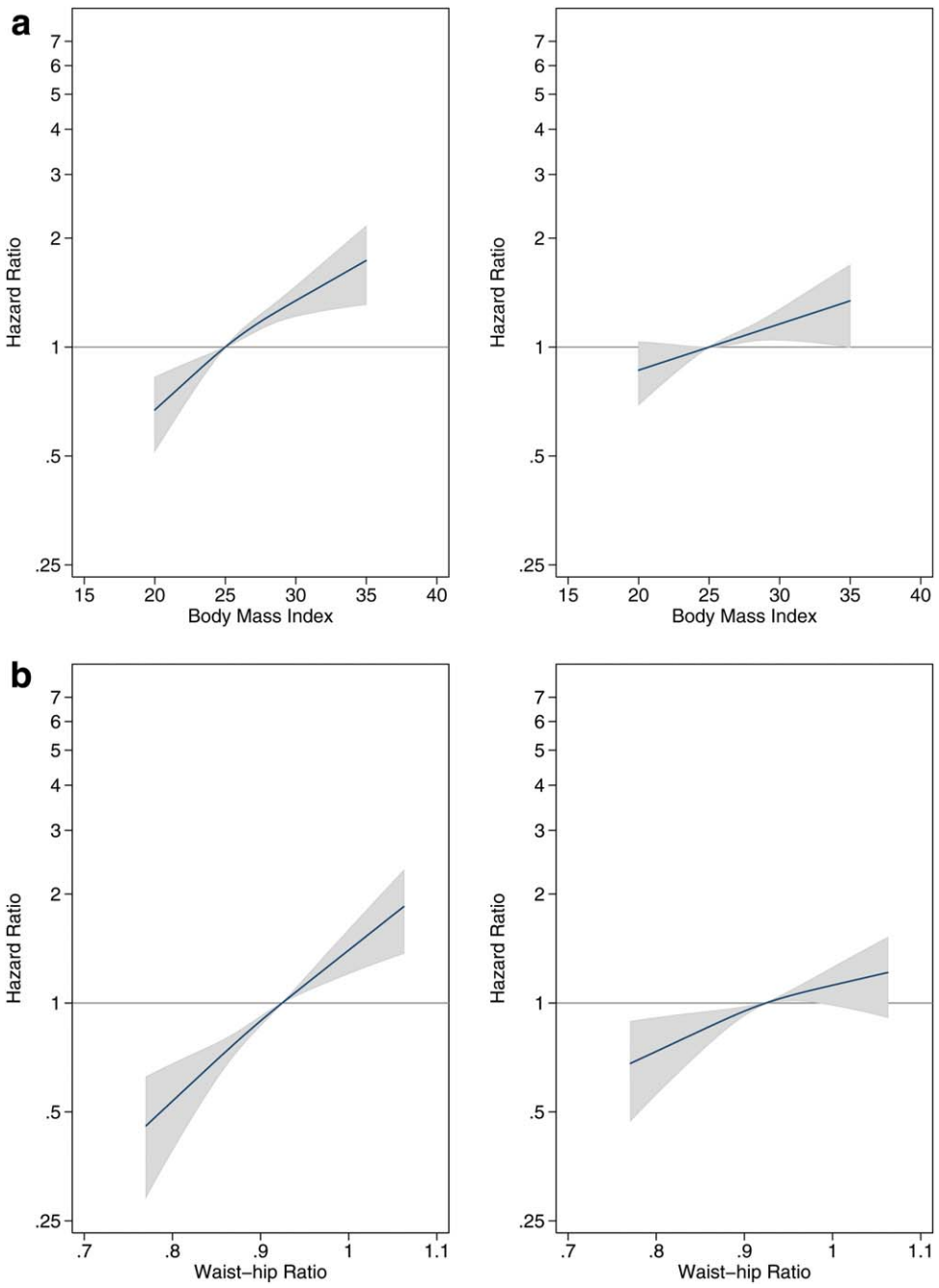

Figure 1 Age-adjusted cubic splines of (**a**) body mass index (BMI) and (**b**) waist–hip ratio (WHR) as predictors of acute myocardial infarction (AMI) in Norwegian men by age group (left figure represents men < 60 years; right figure represents men ≥ 60 years). Median value of each anthropometric measure used as the reference point (HR of 1.0) for graphs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

evaluated with and without BMI as a covariate and, likewise, BMI was evaluated with and without WHR as a covariate. Population attributable fractions (PAF) associated with the top two quintiles of BMI (i.e., ≥ 26.6 kg/m^2 for men and 25.5 kg/m^2 for women) and the top two quintiles of WHR (≥0.91 for men and ≥ 0.80 for women) compared to the lowest three quintiles were calculated in three multivariable models (14-16). Because the magnitude of PAFs is dependent on the percent of the population with the risk factor, the utilization of the top two quintile cutoff (≥40%ile) for BMI and WHR allowed for comparisons between men and women and between the anthropometric measures. The cutoff associated with the top two quintiles in men for BMI (≥26.6 kg/m^2) and for WHR (≥0.91) was only slightly higher than the widely used overweight cutoff for BMI (≥25.0 kg/m^2) and WHO's WHR cutoff for men (≥0.90) (17). For women, the top two quintile cutoffs for BMI (≥25.5) and WHR (≥0.80) were comparable to the overweight cutoff for BMI, but slightly

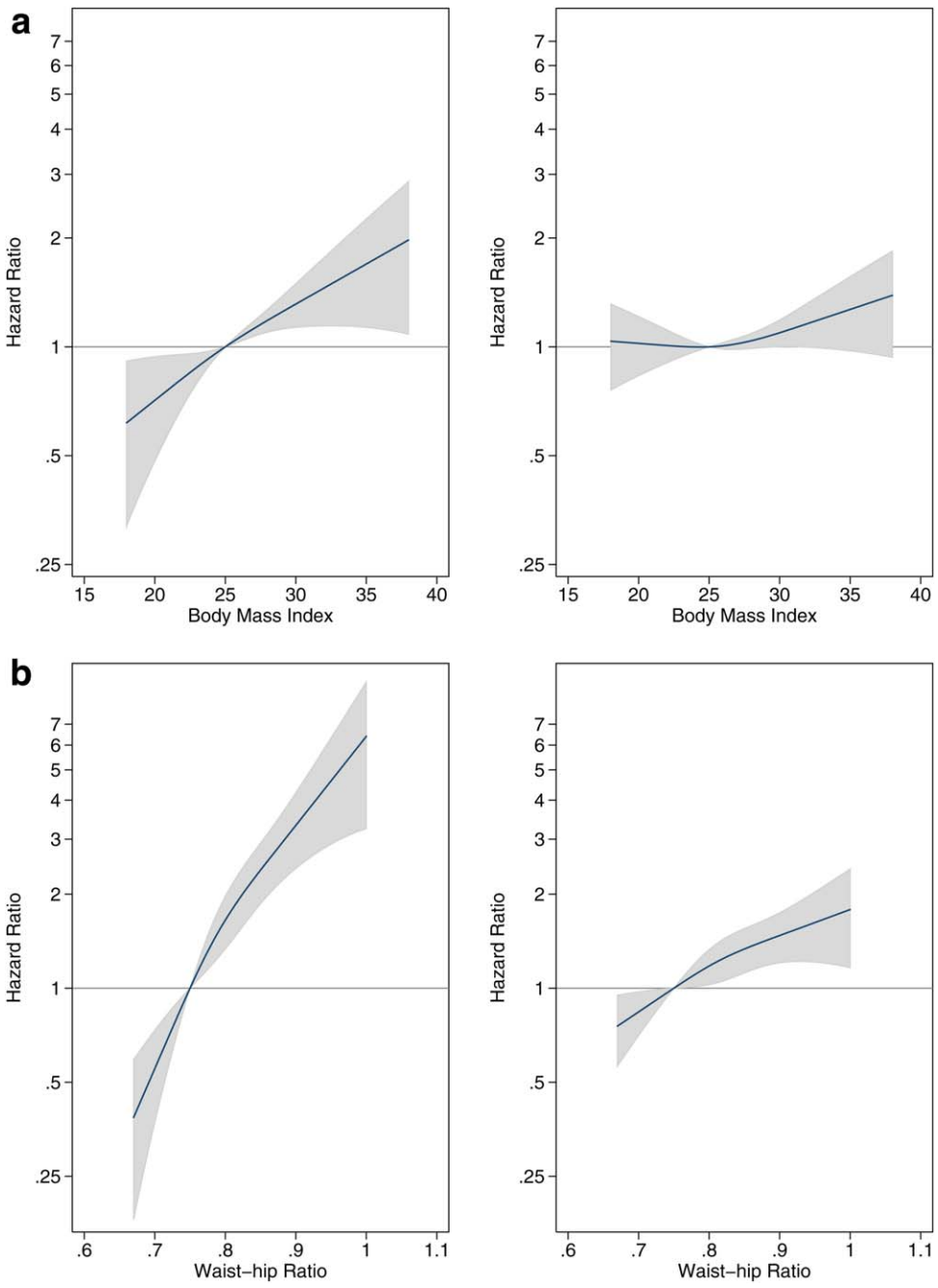

Figure 2 Age-adjusted cubic splines of (**a**) body mass index (BMI) and (**b**) waist–hip ratio (WHR) as predictors of acute myocardial infarction (AMI) in Norwegian women by age group (left figure represents women < 60 years; right figure represents women ≥ 60 years). Median value of each anthropometric measure used as the reference point (HR of 1.0) for graphs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

lower than the WHO cutoff for WHR (≥0.85). For WC, the top two quintile cutoff value in men (≥93.0 cm) and women (≥81 cm) was comparable to the WHO WC cutoff for Europoid men (>94 cm) and women (>80 cm).

The STATA command "*punafcc*" was used to calculate the PAFs and 95% CI (16). STATA *punafcc* calculates the unattributable fraction, which in this case is a mean between-scenario HR. Two scenarios are possible in STATA, the real-world scenario of individuals at risk and not at risk and then a fantasy scenario where no one is at risk. The ratio provides a population unattributable fraction which is then subtracted from 1 to provide the PAF. Significance was determined by $P < 0.05$. Stata 12 (Stata Corp LP, College Station, TX) was used in all analyses.

TABLE 2 Population attributable fractions (PAF) associated with the top two quintiles of BMI and WHR for incident acute myocardial infarction[a] by age and sex: CONOR (N = 140,790)

	< 60 years of age			≥ 60 years of age		
	PAF% (95% CI)[b]	PAF% (95% CI)[c]	PAF% (95% CI)[d]	PAF% (95% CI)[b]	PAF% (95% CI)[c]	PAF% (95% CI)[d]
Men						
BMI top 2 quintiles[e]	16.5 (12.2,20.6)	12.5 (6.6, 17.9)	5.7 (−1.0, 12.0)	10.2 (6.1, 14.1)	6.4 (1.4, 11.1)	0.2 (−5.4, 5.5)
WHR top 2 quintiles[f]	16.8 (11.6, 21.6)	13.2 (7.4, 18.5)	9.3 (3.0, 15.1)	12.1 (6.0, 17.8)	9.2 (2.5, 15.5)	5.4 (−1.7, 12.0)
Women						
BMI top 2 quintiles[e]	20.6 (12.4, 28.1)	15.2 (3.6, 25.5)	6.5 (−7.2, 18.5)	10.4 (3.6, 16.8)	9.4 (0.7, 17.4)	−0.2 (−10.2, 8.9)
WHR top 2 quintiles[f]	32.6 (22.6, 41.4)	28.9 (18.0, 38.4)	26.1 (14.6, 36.1)	11.4 (2.8, 19.2)	8.8 (−0.5, 17.2)	3.2 (−6.8, 12.2)

[a]Ascertained within a mean (SD) of 11.5 (2.8) years of follow-up.
[b]Model includes age (years) and current daily smoking (yes vs. no).
[c]Model includes age (years), current daily smoking (yes vs. no), and WHR and BMI (top two quintiles vs. lower three quintiles).
[d]Model includes age, current daily smoking, WHR and BMI (top two quintiles vs. lower three quintiles), mean systolic blood pressure (mm Hg), self-reported diabetes, and total cholesterol–HDL-C ratio.
[e]Top two BMI quintiles cutoff was ≥26.6 kg/m^2 for men and 25.5 kg/m^2 for women.
[f]Top two WHR quintiles cutoff was ≥ 0.91 for men and ≥ 0.80 for women.
CONOR, Cohort of Norway; CI, confidence interval; BMI, body mass index (kg/m^2); WHR, waist–hip ratio; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation.

Additional analyses

Given that risk factors can change over time resulting in misclassification and biasing estimates toward the null, we conducted a sensitivity analyses restricted to the first 6 years of follow-up using Cox and logistic regression analyses to evaluate consistency in results between these two methods and our overall analyses. We also conducted the analyses limited to those under 50 years of age in which we observed similar results as those presented for participants under 60 years of age but with wider CI (data not presented). We also evaluated the association of WHR by the presence/absence of an enlarged WC in Cox proportional hazards regression, and we present adjusted HR and 95% CI (Online Supporting Information). Finally, we evaluated the BMI-adjusted WC standardized residuals in Cox regressions adjusting for BMI and all covariates. Similarly, we evaluated the WC-adjusted WHR standardized residuals in Cox regressions adjusting for WC and all covariates using the residual regression approach described elsewhere (18).

Results

The mean (SD) follow-up time was 11.5 (2.8) years for both men and women. At baseline, the men and women under 60 years of age had a mean age of 41 (9.0) years; and those 60 years of age or older had a mean age of 70 (7.0) years, ranging up to 98.6 years (Table 1). Older men and women had higher mean values or prevalence of CHD risk factors, with the exception of smoking which was less prevalent among older compared to younger men and women.

For the 66,982 men, 3,219 (4.8%) developed AMI: 1,537 (2.9%) and 1,682 (11.8%) for men under 60 years and 60 years or older, respectively. For the 73,808 women, 1,434 (1.9%) developed an AMI: 441(0.7%) and 993 (7.4%) for women under 60 years and 60 years or older, respectively.

There was a strong and significant correlation between BMI and WC ($r = 0.81$ and 0.85 for men and women, respectively) and between WC and WHR ($r = 0.80$ and 0.78 for men and women, respectively). In contrast, the BMI and WHR correlation, while statistically significant, was not high ($r = 0.54$ and 0.49, for men and women, respectively). To illustrate, there was a considerable degree of discordance between the top two quintiles of BMI and WHR: 63.3% of men and 62.2% of women were either in the top two quintiles of BMI or in the top two quintiles of WHR but not in both risk groups. To avoid colinearity issues, we focused on BMI and WHR in our analyses.

Age-adjusted cubic spline graphs depicted a stronger gradient in risk of AMI associated with BMI and WHR for men and women less than 60 years of age compared to those 60 years of age or older (Figures 1 and 2). Age group by BMI and by WHR interaction terms were significant (Ps < 0.001). Further, the WHR association with AMI was stronger in women than in men (sex by WHR interaction, $P \leq 0.001$). Similar and significant age and sex differences were observed for the association between WC and AMI (Supporting Information Figures 1 and 2).

Population attributable fractions

In age-adjusted analyses, the PAF for AMI associated with a WHR in the top two quintiles, relative to the lower three quintiles, was higher than that associated with having a BMI in the top two quintiles relative to the lower three quintiles in women but not men (Table 2). In multivariable-adjusted analyses, the PAF attributed to WHR was 26.1% (95% CI: 14.6–36.1) in younger middle-aged women in contrast to a PAF of 9.3% (3.0–15.1) in younger middle-aged men after

TABLE 3 Hazard ratios (HR) and 95% confidence intervals (CI) for incident acute myocardial infarction[a] by BMI and WHR quintile groups: CONOR (N = 140,790)

Risk factor	Cases/*N*	% Risk factor	HR (95% CI)[b]	HR (95% CI)[c]	HR (95% CI)[d]
			Men < 60 years of age		
BMI					
≤ 3 quintiles	769/31,729	39.7	1.0 Referent	1.0 Referent	1.0 Referent
≥2 quintiles	764/20,919		1.49 (1.35, 1.65)	1.32 (1.16, 1.50)	1.12 (0.98, 1.29)
WHR					
≤ 3 quintiles	559/26,604	36.0	1.0 Referent	1.0 Referent	1.0 Referent
≥2 quintiles	581/15,550		1.49 (1.32, 1.68)	1.35 (1.19, 1.53)	1.22 (1.07, 1.40)
			Men ≥ 60 years of age		
BMI					
≤ 3 quintiles	909/8,350	41.2	1.0 Referent	1.0 Referent	1.0 Referent
≥2 quintiles	764/5,858		1.28 (1.16, 1.41)	1.17 (1.04, 1.31)	1.01 (0.90, 1.14)
WHR					
≤ 3 quintiles	537/5,317	57.5	1.0 Referent	1.0 Referent	1.0 Referent
≥2 quintiles	863/7,179		1.24 (1.10, 1.38)	1.17 (1.04, 1.32)	1.09 (0.97, 1.23)
			Women < 60 years of age		
BMI					
≤ 3 quintiles	212/37,924	37.0	1.0 Referent	1.0 Referent	1.0 Referent
≥2 quintiles	229/22,222		1.66 (1.37, 2.01)	1.38 (1.09, 1.76)	1.13 (0.88, 1.46)
WHR					
≤ 3 quintiles	122/31,280	36.5	1.0 Referent	1.0 Referent	1.0 Referent
≥2 quintiles	192/17,987		2.16 (1.71, 2.72)	1.91 (1.50, 2.43)	1.76 (1.37, 2.25)
			Women ≥ 60 years of age		
BMI					
≤ 3 quintiles	423/6,196	53.7	1.0 Referent	1.0 Referent	1.0 Referent
≥2 quintiles	558/7,192		1.23 (1.08, 1.40)	1.19 (1.02, 1.39)	1.00 (0.85, 1.17)
WHR					
≤ 3 quintiles	295/5,020	55.8	1.0 Referent	1.0 Referent	1.0 Referent
≥2 quintiles	478/6,348		1.23 (1.06, 1.42)	1.17 (0.99, 1.37)	1.05 (0.90, 1.24)

[a]Ascertained within a mean of 11.5 years (SD 2.8) of follow-up.
[b]Model includes age (years) and current daily smoking (yes vs. no).
[c]Model includes age (years), current daily smoking (yes vs. no), and WHR and BMI (top two quintiles vs. lower three quintiles).
[d]Model includes age (years), current daily smoking (yes vs. no), WHR and BMI (top two quintiles vs. lower three quintiles), mean systolic blood pressure (mm Hg), self-reported diabetes, and total cholesterol–HDL-C ratio.
BMI, body mass index (kg/m^2); WHR, waist–hip ratio; CONOR, Cohort of Norway; SD, standard deviation; HDL-C, high-density lipoprotein cholesterol.

adjusting for BMI (top two quintiles versus lower three quintiles), age, smoking, systolic blood pressure, self-reported diabetes, and the total cholesterol–HDL-C ratio (Table 2). The HRs (95% CI) upon which the PAFs were calculated are provided in Table 3 in which the HR associated with an elevated WHR was stronger in women compared to men.

Additional analyses

In the analyses limited to the first 6 years of follow-up, we observed very similar results between the PAFs based upon logistic regression and the Cox proportional hazards analyses. In these analyses, we observed a greater adjusted PAF (model 3) associated with a WHR in the top two quintiles for younger men (PAF of 14.7%; 95% CI: 3.9–24.3) than that reported for the entire cohort follow-up. For older women, the age- and smoking-adjusted PAF associated with a BMI in the top two quintiles was 17.2%; (95% CI: 7.1–26.1), but after adjustment for conventional risk factors, the results were very similar to those already presented.

Further, in the supplementary analyses of men and women under 60 years of age, an elevated WHR was significantly predictive of AMI in men without an enlarged WC and in women with and without an enlarged WC in analyses adjusting for the conventional risk factors (Supporting Information Table 1). The residual approach also identified that the BMI-adjusted WHR standardized residuals but not the WC standardized residuals were significantly predictive of AMI in men under 60 years (Supporting Information Table 2). For women, similar HRs were observed for the BMI-adjusted WHR and WC standardized residuals. In further analyses, however, the WC-adjusted WHR standardized residuals were a significant predictor of AMI in both men and women in analyses adjusting for WC and all covariates (Supporting Information Table 2).

Discussion

The results provide evidence of age and sex differences in the importance of anthropometric measures as risk factors for CHD in which BMI, WHR, and WC showed a stronger association with AMI in younger compared to older adults, and in which WHR and WC, in particular, had a steeper slope in predicting AMI in women compared to men. The data also indicate that WHR captures a dimension of risk not captured by the presence of an enlarged WC, BMI, or the conventional risk factors. The results have implications for improving the identification of high-risk individuals and for the prediction of the burden of obesity in populations. Reliance only upon BMI or only an enlarged WC would underestimate risk of AMI relative to that of WHR especially for young to middle-aged women.

Our results also suggest that further work is needed to examine the utility of anthropometric measures for older adults. Aging is associated with a number of important body composition changes which would alter the predictive value of anthropometric measures. Aging for example, is associated with a greater laxity in stomach muscles, increases in visceral fat and fat mass, including intramyocellular and hepatic fat, and decreases in fat free mass and height (6-8). While it has been shown that the association between BMI and total mortality weakens with increasing age (19), few studies have systematically compared anthropometric measures' prediction of incident heart disease between younger and older adults. In the collaborative analysis of 58 prospective studies, a 1 SD increase in BMI, WC, and WHR was associated with a higher risk for CHD and ischemic stroke for study participants aged 40-59 at baseline than among those 70 years or older at baseline (20), where attenuation in HR for the oldest relative to the youngest group ranged from 0.75 to 0.81. In a case-control study including participants from 52 countries in the INTERHEART study, there was a greater odds ratio (OR) associated with a 1 SD increase in WHR observed for younger (OR 1.46; 95% CI: 1.40-1.53) compared to older study participants (OR 1.32; 95% CI: 1.27-1.37) (4).

Obesity, particularly central fat patterning, likely contributes to CHD via multiple pathways involving oxidative stress and inflammation, steroid hormones, free fatty acids, and altered production and function of adipocyte-derived hormones (21-23). A higher WHR is a surrogate marker of visceral fat (24), lower physical activity, and reduced muscle endurance and muscle mass in the thighs (25), as well as endocrine perturbations that promote lipid accumulation (26). Further, increasing hip diameter has been independently inversely related to cardiovascular disease (27,28).

Currently, no anthropometric measure is considered in existing risk prediction paradigms for CHD given that obesity-related and physician-treatable metabolic mediators (hypertension, diabetes, dyslipidemia) are already considered. However, in an evaluation of 97 prospective cohorts, BMI-defined obesity remained a significant determinant of risk after adjusting for age, sex, smoking, and the metabolic mediators (29). Our findings add to the evidence that consideration of WHR could be highly advantageous in identifying at-risk individuals and in population projections of the burden of disease for young to middle-aged adults, particularly women.

The strengths of the study include the large, healthy baseline population of adults with an extremely low percent lost to follow-up. Also, our study relied upon anthropometric measures rather than self-reported weight status. One limitation, however, is that we did not have a direct measure of body composition, but these advanced and time-consuming techniques are not feasible in large population-based studies. Another limitation is that our results are based on a homogenous, largely ethnic Norwegian population, precluding the generalizability to other ethnic/racial groups.

Conclusion

WHR identifies individuals at risk for CHD above and beyond conventional risk factors, BMI, or an enlarged WC in middle-aged adults. Further work is needed to discern best practice guidelines for capturing the various dimensions of obesity that contribute to chronic disease risk. The current data add to the available evidence that WHR is a promising indicator in the prediction of CHD risk. O

Acknowledgments

The authors thank Kari Juul, M.A., of CVDNOR for her administrative assistance and database management, and Tomislav Dimoski, M.B.A., at the Norwegian Knowledge Centre for Health Services, Oslo, Norway, for his contributions by developing software necessary for obtaining data from Norwegian hospitals and conducting the data collection and quality assurance of data in this project. KJ and TD were both compensated for their work.

This study used data from the Norwegian Cause of Death Registry. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Cause of Death Registry is intended or should be inferred.

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