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Comparing Anthropometric Indicators of Visceral and General Adiposity as Determinants of Overall and Cardiovascular Mortality

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Abstract

Background: It is unclear which anthropometric obesity indicator best predicts adverse health outcomes. This study aimed to investigate the association of body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHR), and hip-adjusted WC with all-cause and cardiovascular mortality.

Methods: 50045 people aged 40–75 (58% women, median BMI: 26.3 kg /m^2) participated in the population-based Golestan Cohort Study. We used Cox regression to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for the association of obesity indicators with mortality. We also examined the association of these indicators with intermediate outcomes, including hypertension, blood glucose, dyslipidemia, carotid atherosclerosis, nonalcoholic fatty liver, and visceral abdominal fat.

Results: After a median follow-up of 10.9 years (success rate: 99.1%), 6651 deaths (2778 cardiovascular) occurred. Comparing 5th to the 1st quintile, HRs (95% CIs) for all-cause and cardiovascular mortality were 1.12 (1.02–1.22) and 1.59 (1.39–1.83) for BMI, 1.16 (1.07–1.27) and 1.66 (1.44–1.90) for WC, 1.28 (1.17–1.40) and 1.88 (1.63–2.18) for WHtR, 1.44 (1.32–1.58) and 2.04 (1.76–2.36) for WHR, and 1.84 (1.62–2.09) and 2.72 (2.23–3.32) for hip-adjusted WC, respectively. Hip-adjusted WC had the strongest associations with the intermediate outcomes.

Conclusion: Indicators of visceral adiposity (e.g., hip-adjusted WC) were much stronger predictors of overall and cardiovascular mortality than were indicators of general adiposity (e.g., BMI). The full-strength effect of visceral adiposity becomes apparent only when both WC, as a risk factor, and hip circumference, as a protective factor, are individually and simultaneously taken into consideration.

Keywords: Body mass index, Cardiovascular, Hip circumference, Mortality, Obesity, Waist circumference

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Introduction

Obesity, defined as excessive or abnormal fat accumulation, is a global epidemic,[1] and rates of adiposity-related complications, including cardiovascular diseases, are rising quickly worldwide.[2] Using measures of obesity that are most strongly associated with adverse health outcomes is critical for prevention and treatment purposes.[3,4]

Several anthropometric obesity measures—such as body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHR), and hip-adjusted WC— have been used in epidemiologic and clinical studies, but it is unclear which one is the strongest

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predictor of morbidity and mortality.[3] BMI is the most commonly used of these measures.[4] However, BMI primarily represents general adiposity and is confounded by muscle mass, while it is intra-abdominal (visceral) adipose tissue that is most strongly associated with metabolic abnormalities.[4] Some guidelines have suggested WC as the most useful indicator of visceral adiposity.[3,5] Some researchers, however, have suggested that using WC alone may be inadequate without taking into consideration the protective effect of hip circumference (HC), and therefore recommended using WHR[6] or hip-adjusted WC.[7]

We used data from the Golestan Cohort Study (GCS), the first large-scale, population-based study in the Middle-East and Central Asia to examine the association of various anthropometric measures with overall and cardiovascular mortality. Further, we used blood analyses and radiologic data available for subsets of cohort participants to examine the associations of anthropometric measures with intermediate outcomes—such as fasting plasma glucose, blood lipids, hypertension, non-alcoholic fatty liver disease, and carotid atherosclerosis. We also used abdominal ultrasonography and magnetic resonance imaging (MRI) data available for subcohorts to compare the association of anthropometric measures with visceral adipose tissue.

Materials and Methods

Study Design and Population

Between 2004 and 2008, 50045 women and men aged 40–75 from the general population of Golestan Province, northeastern Iran, participated in the GCS. Details of the study methods have been published previously.[8] All participants provided a written informed consent. The study protocol was approved by the ethical review committees of the Digestive Disease Research Institute of Tehran University of Medical Sciences, the US National Cancer Institute, and the International Agency for Research on Cancer.[8]

Data Collection

Baseline data: Trained physicians and nutritionists used structured questionnaires to collect data about demographics, medical history, lifestyle, and physical examination. Anthropometrics were measured after an overnight fast. Weight and height were measured in light clothes, without shoes, in the upright position. WC at the end of normal expiration at the umbilical level and HC at the widest portion of the buttocks were measured horizontally, in a standing relaxed posture with feet close together.

Blood measurements: A random sample of the cohort (n = 11418) participated in a repeated measurement study (2011–2012), for whom blood tests such as fasting plasma glucose and lipid profile, in addition to all anthropometrics, were determined.

Radiologic studies: A total of 1612 persons were randomly selected from the repeated measurement study for ultrasonographic assessment of nonalcoholic fatty liver disease, carotid atherosclerotic plaques, carotid intima-media thickness, and visceral fat thickness. Ultrasound assessments were performed using an Accuvix XQ ultrasound unit (Medison, Seoul, Korea). Non-alcoholic fatty liver disease was defined using an ultrasonographic scoring system.[9] Carotid plaque was defined as a localized thickening of >1.2 mm that did not uniformly involve the whole circumference of the artery.[10] Carotid intima-media thickness of more than 1mm was considered abnormal, indicating atherosclerosis.[10] Visceral fat thickness, a reliable index of visceral obesity, was defined as the distance between the anterior wall of the aorta and the internal face of the rectoabdominal muscle perpendicular to the aorta.[11] Of these participants, 200 persons were randomly selected to investigate visceral adipose tissue, using MRI. The participants underwent an abdominal MRI exam using a 1.5-T unit (Symphony, Siemens, Erlangen, Germany) with an 8-channel phased array body coil. Calculation of visceral fat area was performed on three levels of MRI slices, at the levels of L3-L4, L4-L5, and L5-S1, using semi-automated software. Details of these radiologic measurements have been published previously.[12,13]

Follow-up and Cause of Death Ascertainment

All study participants were followed annually. If a death was reported, all clinical reports and hospital records were collected and a verbal autopsy was completed if needed.[14] Two independent internists determined the cause of death based on the International Classification of Diseases 10th version codes. The two codes were compared, and if they were different, a third more senior internist reviewed the data and determined the final code. The death codes were classified as cardiovascular (I00–I99) and non-cardiovascular.

Statistical Methods

Association of anthropometrics with mortality: We used BMI (body weight/(height-squared) in Kg/m^2), WC, WHtR, WHR, and hip-adjusted WC (i.e., the effect of WC estimated in a model that includes also HC) as anthropometric measures indicating obesity. Cox regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between the anthropometrics with future risk of mortality. We chose age as the time scale to estimate HR based on comparison of individuals at the same age, because age is an important potential confounder and effect modifier (i.e., obesity-mortality association may change with age).[15] Follow-up time extended from the date of cohort enrollment to the date of death, loss to follow-up, or 1 January 2018, whichever came first. We did these analyses with both one standard deviation increase for each

measure and for each quintile of increase, after exclusion of persons with BMI<18.5 kg/m^2 (n = 2410). Basic models were adjusted for sex, ethnicity (Turkmen, others), marital status (married, non-married), place of residence (rural, urban), education (no formal schooling, some formal schooling), wealth score (based on ownership of household appliances,[16] quintiles), physical activity (based on the metabolic equivalent of task per minute/week, tertiles), intake of fruit/vegetables (grams/day, tertiles), and history of tobacco, opium and alcohol consumption. Individuals were considered tobacco users or opium users if they had ever used tobacco products or opium products, respectively, at least once a week for a period of six months. Alcohol drinkers were defined as those who had ever drunk alcohol at least once a month for a minimum of six months. We considered these variables as potential confounders because of their significant effects on all-cause mortality (eTable 1 in Supplementary file 1). As sensitivity analyses, to limit the effects of reverse causality, we re-evaluated the associations after excluding participants with a history of chronic diseases (i.e., heart disease, stroke, cancers, chronic obstructive respiratory diseases, asthma, chronic renal failure, chronic hepatic failure, and tuberculosis). The number of missing values was relatively small (BMI, WC, WHtR, and WHR were missing in <0.02%, physical activity in 0.2%, and vegetable and fruit consumption in 1.7% of participants). Participants with missing data were excluded from the related analyses.

Population attributable fraction: To calculate the proportion of deaths associated with obesity, the population attributable fractions (PAFs) were calculated by comparing risk of death based on the actual distributions with the counterfactual scenarios in which all study participants had 18.5 ≤ BMI < 25 or the other anthropometric measures below the upper limit of the first quintile of the respective distributions.

Intermediate outcomes and visceral fat area: We used logistic regression to estimate the odds ratios of the association between anthropometrics with intermediate outcomes, which included fasting blood glucose, lipid profile, alanine aminotransferase, hypertension, carotid atherosclerotic plaque, carotid intima-media thickness, and nonalcoholic fatty liver disease. We used standardized beta coefficients, from linear regression models, to compare the association of anthropometrics with visceral fat.

P values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were done with Stata statistical software, version 12 (StataCorp, College Station, TX).

Results

The 50 045 participants were primarily women (57.6%), rural residents (80.0%), of Turkmen ethnicity (74.4%), without formal education (70.2%), and married (87.8%). The mean baseline age (SD) was 51.5 (8.5) and 52.7 (9.4) years in women and men, respectively. The median (5th, 95th percentiles) for BMI in this population was 26.3 (18.6, 36.2). The corresponding numbers were 95 (73, 118) for WC, 0.60 (0.45, 0.75) for WHtR, and 0.96 (0.82, 1.09) for WHR. (eTables 2–5).

During 509 980 person-years of follow-up (median of 10.9 years), 6651 deaths from all-causes, 2778 deaths from cardiovascular, and 3277 deaths from non-cardiovascular causes were reported. A final cause of death has not yet been determined for the remaining deaths (n = 596). A total of 467 participants (0.9%) were lost to follow-up.

Table 1 shows the association of the anthropometric measures, classified in quintiles, with overall, cardiovascular, and non-cardiovascular mortality. Significant dose-response relationships were seen for the associations of WHR and hip-adjusted WC with all-cause and cardiovascular mortality, in both sexes. Hip-adjusted WC showed the strongest association with mortality in both sexes. Similar results were seen when we used one standard deviation increase for each measure (eTable 6). When WC and HC were mutually adjusted, the association of WC with mortality became stronger, while the association of HC became inverse (eTable 6). Figure 1 compares HRs (95% CIs) of cardiovascular mortality in various categories of WC and HC.

When participants were categorized by age at baseline (under and over 55 years), hip-adjusted WC remained the strongest predictor for both groups (eTable 7). The associations of anthropometrics with mortality after exclusion of participants with history of chronic diseases (n = 7534) remained largely unchanged (eTables 8–10). In further analyses, the associations of BMI and hip-adjusted WC with mortality were assessed after excluding participants with history of chronic diseases at enrollment, ever tobacco users, ever opium users, and all deaths that occurred in the first 5 years of the study (n = 19651) (eTables 11–12). After these restrictions, the association of both BMI and hip-adjusted WC with mortality strengthened, but the hip-adjusted WC was still far stronger. Hip-adjusted WC was also associated with an increased risk of mortality across strata of BMI (i.e., normal, overweight, and obese) and WHR (i.e., 0.9 – <1 and 1 – <1.1) (eTable 13).

In counterfactual scenarios, normalizing BMI to a range of 18.5 to 25 Kg/m^2 and reducing WC, WHtR, and WHR to the first quintile levels were compared (eTable 14). The optimal scenario was the lowest quintile of WC with the highest quintile of HC, with PAF of 55% (46–63%). In this counterfactual scenario 1528 (1278–1750) of the total 2778 cardiovascular deaths would be preventable, compared to saving only 389 (278–500) deaths for normalizing BMI.

Table 2 shows the associations of anthropometrics with several obesity-related disorders. The patterns mirrored those of mortality. The results for hip-adjusted WC are

Table 1. Comparison between Associations of Anthropometric Measure Quintiles and Mortality*

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for Trend
All-Cause Mortality						
All participants						
BMI	1	0.99 (0.92–1.07)	0.98 (0.90–1.06)	1.02 (0.94–1.11)	1.12 (1.02–1.22)	0.012
WC	1	0.96 (0.88–1.04)	1.01 (0.93–1.10)	1.04 (0.96–1.13)	1.16 (1.07–1.27)	<0.001
WHtR	1	1.01 (0.93–1.10)	1.08 (0.99–1.17)	1.10 (1.01–1.21)	1.28 (1.17–1.40)	<0.001
WHR	1	1.10 (1.00–1.21)	1.15 (1.05–1.27)	1.27 (1.16–1.39)	1.44 (1.32–1.58)	<0.001
Hip-adjusted WC	1	1.09 (1.00–1.19)	1.31 (1.19–1.45)	1.48 (1.33–1.66)	1.84 (1.62–2.09)	<0.001
Women						
BMI	1	0.93 (0.83–1.04)	0.99 (0.88–1.11)	0.95 (0.84–1.08)	1.01 (0.89–1.14)	0.580
WC	1	0.91 (0.81–1.03)	0.98 (0.87–1.11)	1.01 (0.89–1.15)	1.10 (0.98–1.25)	0.009
WHtR	1	0.96 (0.84–1.10)	1.11 (0.98–1.27)	1.08 (0.94–1.23)	1.19 (1.05–1.35)	<0.001
WHR	1	1.19 (1.02–1.39)	1.20 (1.03–1.39)	1.38 (1.19–1.59)	1.54 (1.34–1.78)	<0.001
Hip-adjusted WC	1	1.04 (0.92–1.19)	1.28 (1.11–1.48)	1.47 (1.26–1.73)	1.80 (1.50–2.16)	<0.001
Men						
BMI	1	0.93 (0.84–1.03)	0.95 (0.85–1.05)	1.04 (0.93–1.16)	1.12 (1.00–1.25)	<0.001
WC	1	1.01 (0.90–1.13)	1.02 (0.91–1.14)	1.05 (0.94–1.18)	1.22 (1.09–1.38)	<0.001
WHtR	1	1.03 (0.92–1.16)	1.01 (0.90–1.14)	1.17 (1.03–1.32)	1.24 (1.10–1.39)	<0.001
WHR	1	1.03 (0.92–1.17)	1.12 (0.99–1.26)	1.18 (1.05–1.33)	1.37 (1.22–1.54)	<0.001
Hip-adjusted WC	1	1.12 (0.99–1.26)	1.25 (1.09–1.44)	1.40 (1.19–1.64)	1.70 (1.42–2.04)	<0.001
Cardiovascular Mortality						
All participants						
BMI	1	1.27 (1.13–1.44)	1.41 (1.24–1.60)	1.51 (1.32-1.72)	1.59 (1.39–1.83)	<0.001
WC	1	1.10 (0.96–1.27)	1.41 (1.23–1.61)	1.50 (1.31-1.72)	1.66 (1.44–1.90)	<0.001
WHtR	1	1.18 (1.03–1.36)	1.50 (1.31–1.73)	1.55 (1.34-1.79)	1.88 (1.63–2.18)	<0.001
WHR	1	1.29 (1.10–1.51)	1.39 (1.19–1.62)	1.74 (1.49-2.01)	2.04 (1.76–2.36)	<0.001
Hip-adjusted WC	1	1.27 (1.10–1.47)	1.85 (1.57–2.18)	2.19 (1.84-2.61)	2.72 (2.23–3.32)	<0.001
Women						
BMI	1	1.08 (0.91–1.29)	1.18 (0.99–1.41)	1.21 (1.01–1.46)	1.18 (0.98–1.43)	0.135
WC	1	1.08 (0.89–1.31)	1.19 (0.98–1.44)	1.28 (1.05–1.56)	1.37 (1.13–1.66)	0.001
WHtR	1	1.10 (0.89–1.36)	1.40 (1.14–1.73)	1.35 (1.10–1.66)	1.53 (1.25–1.88)	<0.001
WHR	1	1.41 (1.10–1.80)	1.34 (1.05–1.70)	1.73 (1.37–2.18)	1.91 (1.52–2.40)	<0.001
Hip-adjusted WC	1	1.27 (1.03–1.55)	1.63 (1.30–2.04)	1.98 (1.55–2.53)	2.39 (1.81–3.16)	<0.001
Men						
BMI	1	1.30 (1.08–1.55)	1.57 (1.32–1.88)	1.82 (1.52-2.19)	1.99 (1.65–2.39)	<0.001
WC	1	1.14 (0.93–1.39)	1.50 (1.24–1.82)	1.73 (1.43-2.10)	1.97 (1.62–2.39)	<0.001
WHtR	1	1.16 (0.94–1.44)	1.40 (1.14–1.72)	1.85 (1.51-2.26)	2.01 (1.65–2.46)	<0.001
WHR	1	1.20 (0.97–1.48)	1.40 (1.15–1.72)	1.68 (1.38-2.05)	2.10 (1.73–2.54)	<0.001
Hip-adjusted WC	1	1.23 (1.00–1.52)	1.76 (1.40–2.22)	2.18 (1.68-2.82)	2.61 (1.96–3.49)	<0.001
Non-cardiovascular Mortality						
All participants						
BMI	1	0.87 (0.79–0.97)	0.77 (0.69–0.87)	0.76 (0.67–0.86)	0.84 (0.74–0.95)	0.001
WC	1	0.88 (0.79–0.98)	0.81 (0.72–0.91)	0.80 (0.71–0.90)	0.88 (0.78–0.99)	0.102
WHtR	1	0.90 (0.81–1.01)	0.88 (0.78–0.99)	0.84 (0.75–0.96)	0.94 (0.82–1.07)	0.625
WHR	1	0.97 (0.86–1.11)	1.01 (0.90–1.15)	1.03 (0.91–1.16)	1.10 (0.97–1.24)	0.003
Hip-adjusted WC	1	1.00 (0.89–1.12)	1.04 (0.90–1.20)	1.13 (0.97–1.33)	1.40 (1.17–1.69)	<0.001
Women						
BMI	1	0.82 (0.70–0.97)	0.82 (0.69-0.97)	0.76 (0.63–0.91)	0.86 (0.72–1.03)	0.238
WC	1	0.82 (0.69–0.98)	0.85 (0.71-1.01)	0.85 (0.71–1.02)	0.94 (0.78–1.12)	0.792
WHtR	1	0.91 (0.76–1.10)	1.01 (0.84-1.22)	0.91 (0.76–1.10)	1.01 (0.84–1.22)	0.275
WHR	1	1.05 (0.85–1.31)	1.15 (0.93-1.41)	1.26 (1.03–1.54)	1.38 (1.13–1.70)	<0.001
Hip-adjusted WC	1	0.95 (0.79–1.15)	1.15 (0.93-1.41)	1.32 (1.05–1.67)	1.66 (1.27–2.17)	<0.001
Men						
BMI	1	0.80 (0.70–0.92)	0.74 (0.63–0.85)	0.72 (0.62–0.85)	0.73 (0.62–0.87)	0.001
WC	1	0.97 (0.84–1.12)	0.78 (0.67–0.91)	0.75 (0.64–0.88)	0.85 (0.72–1.00)	0.025
WHtR	1	0.96 (0.82–1.12)	0.86 (0.73–1.01)	0.86 (0.73–1.02)	0.85 (0.72–1.00)	0.107
WHR	1	0.93 (0.79–1.09)	0.96 (0.82–1.12)	0.91 (0.78–1.07)	0.95 (0.81–1.12)	0.888
Hip-adjusted WC	1	1.07 (0.91–1.25)	0.94 (0.78–1.14)	0.95 (0.76–1.19)	1.16 (0.89–1.50)	0.042

Abbreviations: BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio.
*After exclusion of participants with BMI<18.5 kg/m^2. Data are hazard ratios (95% confidence intervals), with age as the time scale, adjusted for ethnicity, residence, marital status, education, wealth score, physical activity, tobacco use, opium use, alcohol drinking, fruit/vegetable consumption, and sex, if applicable. *P* for trends are based on continues variables. Quintile cut-points for all measures are shown in supplementary eTable 4.

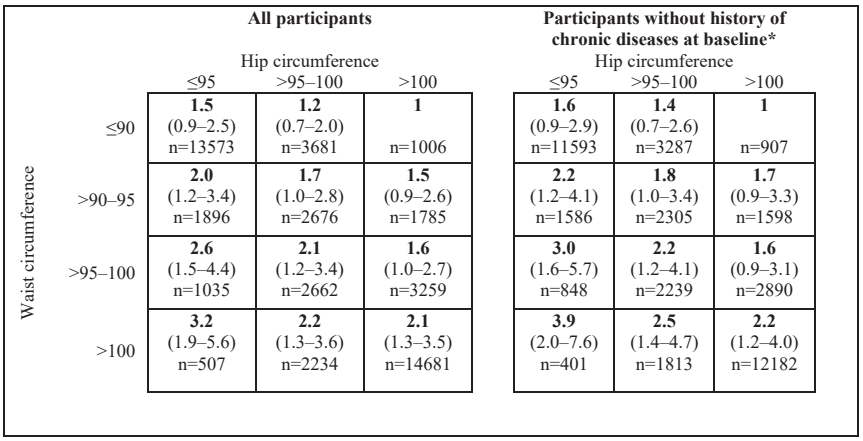

Figure 1. Association of Waist and Hip Circumferences with Cardiovascular Mortality. Data are HRs (95% CIs). Cox regression models were used, with age as the time scale, adjusted for sex, ethnicity, residence, marital status, education, wealth score, physical activity, tobacco use, opium use, alcohol drinking, and fruit/vegetable consumption. *History of chronic diseases was defined as a history of heart disease, stroke, cancers, chronic obstructive respiratory diseases, asthma, chronic renal failure, chronic hepatic failure, and tuberculosis.

the most interesting because this was the variable with the strongest association with mortality.

Table 3 shows the association of anthropometrics with visceral fat. Similar to patterns observed with mortality, hip-adjusted WC had the strongest association with visceral fat.

Discussion

Anthropometric measures that included HC (i.e., hip-adjusted WC and WHR) performed better in predicting mortality than other measures including BMI, WC, and WHtR, especially in the lower quintiles. Among them, hip-adjusted WC had the strongest association with all-cause and cardiovascular mortality. The significant effect of hip-adjusted WC was seen in both sexes and younger and older ages. By contrast, the relation of BMI with mortality was weak and less consistent, especially in women. Similar patterns were observed when we used intermediate outcomes—including plasma glucose, lipid profile, alanine aminotransferase, hypertension, non-alcoholic fatty liver disease, and carotid atherosclerosis—instead of mortality. Likewise, hip-adjusted WC had the strongest correlation with visceral adiposity.

Our study supports findings that visceral adiposity is a more important predictor of morbidity and mortality than general adiposity.[3,4,6,7] Visceral adipocytes have properties that are different from subcutaneous adipocytes. For example, visceral adipocytes are less differentiated, have lower expression of cardio-protective adipokines and higher expression of pro-inflammatory adipokines, and have reduced adipogenesis potential.[17] Visceral adiposity can provide an overflow of free fatty acids, via the portal vein, to the liver, leading to metabolic abnormalities, including insulin resistance and dyslipidemia.[4] It is hypothesized

Table 2. Effects of One Standard Deviation Increase in Anthropometrics on Intermediate Outcomes

	BMI	WC	WHtR	WHR	Hip-Adjusted WC
FBS (≥100 mg/dL), (2505/8479)[a]	1.38 (1.31–1.46)	1.48 (1.41–1.56)	1.54 (1.45–1.62)	1.53 (1.45–1.61)	1.92 (1.76–2.10)
Total cholesterol (≥200 mg/dL), (4522/8792)[a]	1.23 (1.17–1.29)	1.27 (1.21–1.33)	1.31 (1.25–1.38)	1.31 (1.25–1.37)	1.49 (1.38–1.61)
LDL-cholesterol (≥100 mg/dL), (6074/8640)[a]	1.23 (1.16–1.30)	1.27 (1.21–1.34)	1.31 (1.24–1.38)	1.30 (1.24–1.37)	1.46 (1.34–1.60)
HDL-cholesterol (<50 mg/dL), (2259/8943)[a]	1.31 (1.24–1.39)	1.44 (1.36–1.52)	1.41 (1.33–1.50)	1.54 (1.46–1.63)	1.98 (1.81–2.17)
Triglycerides (≥150 mg/dL), (2657/8958)[a]	1.57 (1.49–1.65)	1.78 (1.68–1.87)	1.79 (1.6–1.89)	1.93 (1.83–2.04)	2.69 (2.46–2.94)
ALT (≥40 U/l), (881/9029)[a]	1.47 (1.36–1.58)	1.60 (1.48–1.73)	1.67 (1.54–1.82)	1.68 (1.56–1.82)	2.22 (1.95–2.52)
Hypertension[b] (10720/34553)[a]	1.52 (1.48–1.57)	1.52 (1.48–1.56)	1.56 (1.52–1.61)	1.41 (1.37–1.45)	1.59 (1.53–1.67)
Carotid atherosclerotic plaque, (567/1234)[a]	1.17 (1.03–1.33)	1.12 (.99–1.27)	1.24 (1.08–1.42)	1.18 (1.04–1.33)	1.28 (1.06–1.55)
Carotid IMT (>1 mm), (82/1232)[a]	1.04 (0.80–1.35)	0.97 (0.77–1.24)	1.04 (0.79–1.37)	1.05 (0.82–1.34)	1.13 (0.76–1.69)
NAFLD, (504/1235)[a]	2.65 (2.27–3.10)	2.92 (2.49–3.42)	3.23 (2.71–3.85)	2.54 (2.18–2.97)	4.15 (3.26–5.29)

Abbreviations: BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio; FBS, fasting blood glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine aminotransferase; IMT, intima-media thickness; NAFLD, nonalcoholic fatty liver disease. Data are Odds ratio (95% confidence intervals) adjusted for age and sex.

[a] Number of outcome positive/all participants; after exclusion of participants with BMI<18.5 kg/m^2 and/or history of chronic diseases; for FBS analyses, after exclusion of participants with anti-diabetes drugs; for total cholesterol and LDL-cholesterol, after exclusion of participants with statin drugs; for HDL-cholesterol and triglycerides, after exclusion of participants with fibrates and nicotinic acid.

[b] Systolic blood pressure ≥ 140 or diastolic blood pressure ≥90 mm Hg, after excluding persons with history of antihypertensive drug use.

Table 3. Association between Visceral Adipose Tissue and Anthropometrics

Anthropometric in the Models[a]	Based on Magnetic Resonance Imaging Data			Based on Ultrasonography Data		
	All (n = 191)	Women (n = 95)	Men (n = 96)	All (n = 1609)	Women (n = 782)	Men (n = 827)
BMI	0.60[b]	0.51[b]	0.69[b]	0.70[b]	0.63[b]	0.72[b]
WC	0.69[b]	0.67[b]	0.77[b]	0.73[b]	0.70[b]	0.75[b]
HC	0.42[b]	0.29	0.58[b]	0.51[b]	0.43[b]	0.61[b]
WHtR	0.70[b]	0.60[b]	0.71[b]	0.81[b]	0.71[b]	0.75[b]
WHR	0.59[b]	0.64[b]	0.63[b]	0.60[b]	0.55[b]	0.66[b]
WC and HC						
WC (hip-adjusted)	0.74[b]	0.78[b]	0.77[b]	0.84[b]	0.82[b]	0.83[b]
HC (waist-adjusted)	-0.08	-0.19	-0.01	-0.14[b]	-0.17[b]	-0.09
BMI, WC, and HC						
WC (hip and BMI-adjusted)	0.68[b]	0.77[b]	0.67[b]	0.63[b]	0.57[b]	0.62[b]
HC (waist and BMI-adjusted)	-0.13	-0.20	-0.07	-0.31[b]	-0.41[b]	-0.19[b]
BMI (waist and hip-adjusted)	0.12	0.03	0.17	0.39[b]	0.48[b]	0.32[b]

Abbreviations: BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio; HC, hip circumference.
Data are standardized beta coefficients.
[a] Linear regression models adjusted for age and sex, if applicable.
[b] $P < 0.001$.

that subcutaneous fat can act as a "metabolic sink" to buffer energy excess, protecting other tissues from a lipid overflow.[4] As such, a reduced capacity of subcutaneous fat to store excess energy would result in ectopic fat deposition, i.e., accumulation of fat at undesirable sites such as visceral adipose tissue, liver, skeletal muscle, and heart.[4]

Researchers have debated using WC versus a combination of WC and HC as markers of future disease risk. The World Health Organization (WHO)[3] and the American Heart Association[2] have been in favor of using WC over WHR, primarily because of the relative ease of measuring WC alone, and also because there have been fewer thoroughly conducted studies on WHR effects. However, WC may not adequately distinguish subcutaneous from visceral abdominal fat, as they both contribute to higher WC. Liposuction of subcutaneous abdominal fat resulted in reduction in WC but has no effect on metabolic abnormalities caused by visceral fat.[18] A study showed that higher HC could be a marker of higher deposition of subcutaneous fat, not only in the hips but also in the abdomen. So for a given WC, individuals with a higher HC, have less visceral fat.[19] HC is also correlated with gluteal and total leg muscle, a proxy measure of physical activity, which has cardio-protective effects.[20] Furthermore, several studies have found protective effects of HC and advocate for using measures that can use information from both WC and HC.[6,7,21] Our study confirmed that without considering HC, the effect of WC on morbidity and mortality is underestimated.

Combining WC and HC data can be done using WHR or by entering both WC and HC in analytic models. Not only did we find a stronger association of mortality with hip-adjusted WC, but we were also able to observe the effect of HC, after adjustment for WC. Similar findings have also been reported in studies from other countries such as the United Kingdom,[22] Denmark,[23] Norway,[24] and people of South Asian and African descent in Mauritius.[25] Because WC and HC are correlated, the full-strength effect of these variables become apparent only when both are individually (not as a ratio) entered in the models.[7] Using WHR may be problematic for monitoring or comparison purposes.[20,26] For example, a WHR of 0.83 may mean WC and HC of 100 and 120 cm, or a WC and HC of 75 and 90 cm, respectively, which may have pose different levels of risk.[4] In addition, using ratios (e.g., WHR) has several limitations such as: (*a*) ratios do not take into consideration the unique properties of the numerator or denominator, such as nonlinear relationships between them[27,28]; (*b*) the effects of covariates/confounders associated with WC and HC may not be the same, and combining them as a ratio may not properly adjust for them[23]; and (*c*) WC and HC reflect different biological constituents. These limitations of WHR should also be considered for WHtR.

In our study, increase in BMI had only a weak association with overall and cardiovascular mortality. BMI does not distinguish lean mass from fat mass and does not recognize fat distribution.[2] In different populations, it may not reflect the same degree of adiposity due, in part, to different body proportions.[29] To alleviate some of the deficiencies of BMI, a recent study suggested that, in addition to body weight, the body composition (e.g., lean body mass) should be considered.[30] Some researchers have conducted analyses by excluding participants with a history of chronic diseases at baseline, ever smokers, and deaths within the first 5 years of follow-up to take into consideration reverse causality and residual confounding.[31] Other researchers disagree with such wide restrictions, because of generalizability problems, substantially reduced sample size, and lack of

effect consistency across studies.[32] In our study, after these restrictions, the BMI-mortality association remained nonsignificant in women. Further, after adjusting for HC, the association of BMI with mortality became stronger, while after adjusting for WC, the associations became inverse (eTable 6). Also, after simultaneously adjusting for both WC and HC, the association of BMI with visceral adipose tissue decreased (Table 3). Collectively, these analyses indicated that the most, if not all, risk effects of general obesity are due its visceral component.

Our study has several strengths. To our knowledge, this is the first large scale prospective study of anthropometrics in relation to mortality from the Middle-East and Central Asia. Data were available from a population-based prospective study with over 500 000 person-years of follow-up and an over 99% rate of successful follow-up. We had a comprehensive dataset, including several anthropometric measures, covariates, radiologic measurement of visceral adipose tissues, and a variety of intermediate outcomes. We directly measured all anthropometrics, because errors in self-reported measurement are important sources which could bias the results.[33] We aimed at avoiding over-adjustment– which can happen by adjusting for factors in causal pathway such as hypertension—as well as under-adjustment—which may happen because of lack of adjusting for significant variables such as socioeconomic factors. However, some limitations still exist. Residual confounding resulting from measurement error (e.g., physical activity, wealth score, and vegetable and fruit consumption) is a limitation for this study. However, this issue is likely to have affected all adiposity measures, therefore, it is unlikely to have generated the better performance of hip-adjusted WC. Small numbers of events for some subgroup analyses and outcomes, such as specific cardiovascular diseases, precluded further detailed analyses. WC was measured at the umbilical level, different from WHO guideline, which is the midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid-axillary line.[3] However, a systematic review of 120 studies showed that measurement methods had no substantial influence on the association between WC and cardio-metabolic risk.[34]

Our findings have some important implications for epidemiologic studies, risk prediction, medical interventions, and outcomes definition in clinical trials. For epidemiologic studies, our findings suggest that using hip-adjusted WC is superior to BMI, WC, WHtR, and WHR as a predictor of all-cause and cardiovascular mortality. Further studies about HC and WC, simultaneously, may affect guidelines recommendations about the appropriate cutpoints for WC. To enhance convenience, affordability, and availability, especially in low-resource settings, researchers have embarked on designing risk prediction charts that do not require laboratory tests by, for example, substituting BMI for cholesterol and diabetes.[35,36] If our results are replicated, including WC and HC in the models, may substantially improve such risk prediction models. In clinic and for clinical trials, we suggest considering separate measurement of WC, as a risk factor, and HC, as a protective factor. A recent clinical trial showed that exercise resulted in visceral fat reduction, irrespective of weight loss.[37] Also, an isocaloric Mediterranean low-carbohydrate diet was superior to an isocaloric low-fat diet in reduction of visceral fat.[37] Thus, where possible, lifestyle modifications that more precisely target reduction of visceral adiposity are superior to those that target total body weight.

In conclusion, hip-adjusted WC was a very strong predictor of all-cause and cardiovascular mortality in a Middle-Eastern/Central Asian population, while BMI was not.

Authors' Contribution

MN, SM, CA, FK, HP, SS, SD, RM, MSo, PBo, AP, AE, and PBr conception and design; AR, HP, AP, AE, MSh, MK, AG, RS, and AN acquisition and interpretation; MN, FK, SS, SD, PBo analysis and interpretation; MN, FK, SS, RM, and MSh drafted manuscript; SM, MSo, CA, AR, HP, SD, PB, AP, AE, MK, AG, RS, AN, and PBr critically revised manuscript; all authors gave final approval and agree to be accountable for all aspects of the paper.

Conflict of Interest Disclosures

The authors declare no competing interests.

Ethical Statement

We have written ethical statements in the first paragraph of the "Materials and Methods" section.

Role of the Funding Source

The founders of the study had no role in study design, data collection, analysis, and interpretation, or writing of the report. MN, RM, and FK had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Supplementary Materials

Supplementary file 1 contains eTables 1-14.

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