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Body mass index, waist circumference, and waist-hip ratio: which is the better discriminator of cardiovascular disease mortality risk? Evidence from an individual-participant meta-analysis of 82,864 participants from nine cohort studies

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Abstract

Few studies have examined both the relative magnitude of association and the discriminative capability of multiple indicators of obesity with cardiovascular disease (CVD) mortality risk. We conducted an individual-participant meta-analysis of 9 cohort studies of men and women drawn from the British general population resulted in sample of 82,864 individuals. Body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) were measured directly. There were 6,641 deaths (1,998 CVD) during a mean of 8.1 years of follow-up. After adjustment, a one SD higher in WHR and WC was related to a higher risk of CVD mortality (HR (95% CI)): 1.15 (1.05-1.25) and 1.15 (1.04-1.27), respectively. The risk of CVD also increased linearly across quintiles of both these abdominal obesity markers with a 66% increased risk in the highest quintile of WHR. In age- and sex-adjusted models only, BMI was related to CVD mortality but not in any other analyses. No major differences were revealed in the discrimination capabilities of models with BMI, WC or WHR for cardiovascular or total mortality outcomes. In conclusion, measures of abdominal adiposity, but not BMI, were related to an increased risk of cardiovascular disease mortality. No difference was observed in discrimination capacities between adiposity markers.

Keywords

body mass index; waist circumference; waist-to-hip ratio; cardiovascular disease mortality

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Introduction

There has been a well documented increase in the prevalence of overweight and obesity in developing and developed countries, with over one billion adults worldwide meeting current definitions for excess weight(1). The role of overweight and obesity in the aetiology of cardiovascular disease (CVD) risk has a long research tradition(2). Using body mass index (BMI, kg/m²) as a marker of excess body fat accumulation, studies have revealed null, linear, J- or U-shaped relationships with mortality risk(3-5).

BMI comprises a combination of both fat mass and fat free mass which have opposing effects on health(6). Hence, more recently, investigators have examined the predictive significance of abdominal adiposity markers, such as waist circumference (WC) and waist-hip ratio (WHR), for CVD risk. Based on the few studies conducted, there is a suggestion that the adiposity-CVD association is strongest for WHR followed by WC then BMI(7-12).

However, a number of outstanding issues remain. First, it is unclear if the impact of each indicator of adiposity on CVD mortality is independent of the effects of potential mediating factors, such as blood cholesterol, diabetes, and blood pressure. Second, beyond comparison of areas under the curves - an insensitive approach - no prospective study has, to our knowledge, assessed the difference in discriminative capability of these adiposity markers for CVD mortality. Recent statistical techniques, such as the relative integrated discrimination improvement (RIDI %) statistic, potentially represent a major advance in assessing differences in the performance of predictive models but have yet to be well utilised in this area(13;14). The aim of the present study is examine these two outstanding research questions on all-cause and CVD mortality, using a pooled analysis of a series of 9 cohort studies of men and women drawn from the British general population.

Methods

Participants were drawn from 9 cross-sectional UK surveys comprising of the Scottish Health Surveys (SHS, 3 cohorts) and the Health Survey for England (HSE, 6 cohorts). Sampling individuals living in households in each country, all studies are representative of the general population. The characteristics of the individual cohorts are presented in table 1. The mean age at baseline ranged between 49 and 57 years, with women marginally comprising the majority of study members (range: 54-62%). Study participants gave full informed consent and ethical approval was obtained from the London Research Ethics Council or the Local Research Ethics Councils.

The full protocols for the HSE and SHS data collection have been described in detail elsewhere(15;16). In brief, study members were visited twice in their homes. During the first visit, trained interviewers collected data on demographics and health behaviours, including socioeconomic status (as indexed by occupational social class), self-reported smoking, and physical activity. During the second visit, conducted within a few days of the first, nurses gathered clinical data. In the seated position and after five minutes rest, systolic and diastolic blood pressure was measured on three occasions using an Omron HEM-907; an average of the second and third readings was used in the present analyses. Nurses also collected

information about physician-diagnosed CVD (stroke, ischemic heart disease, angina symptoms), other medical conditions (hypertension and diabetes), and blood-pressure lowering medication (beta-blockers, angiotensin converting enzyme-inhibitors, diuretics, calcium blockers).

Height and weight were measured directly by the interviewers using Chasmors stadiometers (Chasmors Ltd., London, UK) and Tanita electronic digital scales (Tanita Incorporation, Japan), respectively. Body mass index (BMI) was calculated using the usual formulae (weight [kg]/height[m]²). Waist and hip circumferences were measured using a tape with an insertion buckle at one end. Waist circumference was measured at the midpoint between the lower rib and the upper margin of the iliac crest. Hip circumference was denoted by the widest circumference around the buttocks, below the iliac crest. Both measurements were taken twice, using the same tape, and were recorded to the nearest even millimetre. Those whose two waist or hip measurements differed by more than 3 cm had a third measurement taken. The mean of the two valid measurements was used in our analysis. For waist and hip measurements all those who reported that they had a colostomy or ileostomy, or were chairbound or pregnant, were excluded from the measurement. All those with measurements considered invalid by the nurse, for example due to refusals to remove excessive clothing or movement, were excluded from the analysis.

Ascertainment of disease-specific mortality

Consenting study members (73,219, 88%) were linked to National Health Service mortality records from which a death certificate was located. Classification of the underlying cause of death was based on information on the death certificate together with any additional observations made by the certifying physician. Diagnoses for primary cause of death was made using the ninth and tenth revisions of the International Classification of Diseases with 390-459 (ICD-9) and IO01-I99 (ICD-10) denoting cardiovascular disease deaths.

Statistical analysis

Cox proportional hazard regression models were used to estimate the hazard ratio (HR) and accompanying 95% confidence intervals (95% CIs) for a one standard deviation (SD) higher in each anthropometric index in relation to the risk of total and CVD mortality. Cox models were used to compute the HRs for the participants in the upper quintiles as compared to those in the lower quintiles of each anthropometric variable. Corresponding 95% CIs were calculated by the floating absolute risk method(17), in order to provide a CI for the reference group, chosen here as lowest level of each anthropometric variable. Log-linearity of the associations between each anthropometric variable was explored both by fitting the fifths of each anthropometric variable and by fitting a continuous predictor that takes the value of each fifth for each participant within that fifth. The likelihood ratio chi square from the model with the continuous predictor and its difference from that of the model with fifths of each variable were then used to characterise the linearity and non-linearity of the association respectively. Baseline models were adjusted for age and sex, followed by socio-economic status, cigarette smoking, systolic blood pressure, total blood cholesterol, diabetes status, physical activity and history of CVD. In preliminary analyses based on individual studies, the relationship between each of the three adiposity indicators and mortality were in the

same direction. There was also no strong evidence for effect modification by gender. We therefore pooled the data, stratified by cohort and adjusted for gender and other covariates.

The ability of anthropometric variables to discriminate between participants who developed an event during follow-up and those who did not was assessed using area under the receiver operating characteristic curves (AUC) and the relative integrated discrimination improvement (RIDI), which measures the percentage increased discrimination when an extra variable is added to a prediction model(13;18). RIDI indicates the magnitude of improvement in the performance of a model that is attributable to adding a further variable, as compared with to the average of predictors already present in the model. RIDI is a continuous variable that can take both positive and negative values. No improvement is indicated by a value of zero. AUC comparisons were examined with nonparametric methods(19). Bootstrap techniques were used to derive the 95% CI for the RIDI estimates which were based on 1000 replications. The likelihood ratio χ^2 statistics for each event category were calculated by comparing multivariate regression models with and without a single anthropometric variable to assess improvement in model fit. Additional analyses were conducted to ascertain the combination of anthropometric variables (BMI+WC or BMI +WHR) and BMI², WC² or WHR² in the Cox models. All analyses used SAS software v.9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Selection of the analytical sample and characteristics of each study contributing to the present meta-analysis are presented in Table 1 and Figure 1. A comparison was made of the baseline characteristics of men and women included in the present analytical sample versus those excluded (Table 2). As a result of missing data and lack of consent for mortality follow-up, around a quarter of the starting sample was excluded. Owing to the large sample size, the differences between these two groups attained statistical significance at conventional levels for all of the listed variables, however, importantly, the absolute differences were very small and not in a consistent direction.

A mean of 98.7 months of mortality surveillance gave rise to 6641 deaths, 1998 of which were ascribed to CVD. As anticipated, established risk factors for CVD were also predictive in the present pooled analyses (Table 3). Thus, CVD mortality risk was elevated in study members who were male, had increased age and systolic blood pressure, lower HDL cholesterol, had a history of diabetes or CVD and who were smokers. The magnitude of these relationships with total mortality was typically lower.

Figures 2 (age- and sex-adjusted analyses) and Figures 3 (fully-adjusted analyses) depict the association of the three indicators of adiposity with total (figures in upper row) and CVD mortality (figures in lower row). While a higher BMI appeared to confer protection against total mortality [HRs (95% CI) for a one higher SD in BMI: 0.95 (0.91-0.99)] in a fully-adjusted model (Figure 3), it was not related to CVD death. However, the markers of visceral obesity were consistently positively associated with the risk of total and CVD mortality. A higher magnitude of association was generally observed for WHR than for WC. For example, in age- and sex-adjusted analyses, the risks for CVD mortality was 1.35

(1.27-1.43) and 1.24 (1.18-1.30) for each higher SD in WHR and WC, respectively (Figure 2). For fifths of each adiposity variable, a 'J'-shaped curve was evident for BMI and CVD mortality. On comparing the top fifth with the bottom one, again, WHR was most strongly associated with total and CVD mortality. Sensitivity analyses excluding study members with a CVD event recorded during the first three years of follow-up did not materially alter these results (data not shown but available upon request).

As presented in Table 4, we examined the predictive value of anthropometric variables for these outcomes by calculating the area under the receiver operating characteristic curves (AUC). There was no major difference in AUCs between the three anthropometric variables, nor when comparing combinations of variables or testing for BMI², WC² or even WHR² (data not shown). Using the RIDI statistics (Table 5), a significant but marginal increase (< 1%) in discrimination capacity was observed when baseline WHR was substituted for body mass index. These results indicate a very modest enhancement in the discriminative capability of the models using WHR instead of BMI. The advantage of using WHR instead of WC was also marginal. Models combining two anthropometric variables such as BMI and WC, or BMI and WHR, did not provide improvements in the prediction of mortality.

Discussion

The aims of this study were two-fold: first, to examine if the association of each indicator of adiposity with CVD mortality was independent of potential mediating factors such as blood cholesterol, diabetes, and blood pressure. Second, to evaluate the difference in discriminative capability of BMI, WC and WHR for CVD mortality.

In this large, well characterised individual-participant meta-analysis of 9 cohorts we found that measures of central adiposity were associated with an increased risk of cardiovascular disease mortality. In a fully-adjusted model, taking into account potential mediating variables such as systolic blood pressure and diabetes status, the effects were not statistically significant at conventional levels for BMI. This suggests that some, if not all, of the impact of BMI on CVD risk occurs via these variables. In all models, WHR showed the strongest association with CVD mortality compared to either WC or even BMI. The present dataset also confirmed the expected associations for a range of established CVD risk factors that strengthen the validity of our findings. Overall comparison of the discrimination capacity of the three adiposity indices revealed no difference using the AUC and a marginal benefit when using the relative integrated discrimination improvement (RIDI) statistics.

Study strengths and limitations

The present study has a number of strengths, including direct measurement of anthropometric markers, the range of covariates available, and our use of recently developed discriminative statistical techniques. Indeed, the AUC has been the most frequently used tool to discriminate between competing models. However, some limitations of the AUC have been suggested and more recently, the RIDI statistic has been proposed for assessing differences in the performance of predictive models. These differences in statistical techniques may explain discrepancies between study results as we previously observed when comparing blood pressure variables in individuals with type 2 diabetes(18). However, in the

current report, the benefit of the RIDI did not provide competing results compared to AUCs. Some limitations also need to be mentioned. Our cohorts, while representative of the people living in Scotland and England, were not sufficiently ethnically diverse to facilitate extrapolation to all ethnic groups. It is also the case that, as described, a series of covariates were measured, but there were insufficient blood analytics for inclusion in the present analyses. Excluded participants tended to have less favourable risk factor profiles than those included, which is often the case in large population based studies. Our results may therefore have underestimated the true risks associated with adiposity.

Comparison with previous studies

The links between obesity and all-cause or cardiovascular disease mortality has been debated in the last two decades with an advisory committee from the American Heart Association recently summarized the findings(20). Methodological issues explain the apparent opposing directions of association observed between BMI and mortality across studies. Among the potential sources of bias is the inability to take into account pre-existing diseases such as smoking-related cancers (reverse causality) that may partially explain the U- or J-shaped relationship between BMI and mortality. Previous meta-analyses investigating the association with BMI and mortality concluded that removing early death occurring during follow-up or taking into account pre-existing disease was not sufficient to modify the shape of the association between body mass index and mortality(5;21). This was also observed in our analyses.

In age- and sex-adjusted models, we observed that when using either a continuous or categorical coding, BMI was related to CVD mortality. This was not evident after adjustment for intermediary variables in the fully-adjusted models. For both levels of adjustment, the associations followed a 'U'- or 'J'-shaped curve. Such an observation was also described in a recent pooled analysis of over one million white adults (1). Thus, in the total population, BMI followed a 'J'-shaped relationship that did not attain statistical significance with all cause mortality until a BMI of $> 30 \text{ kg/m}^2$, especially in men. When restricting the analyses to healthy subjects who never smoked, the 'J'-shaped remained but significant associations were also seen at lower levels of BMI $> 25 \text{ kg/m}^2$. This large new study emphasizes the importance of taking into account prevalent illness (reverse causality) but also the role of smoking. Another potential hypothesis for the non-linear association is that BMI does not take into account for the potentially different role for fat mass and fat-free mass. For example, findings from the Paris Prospective Study(2) supported the differential impact of body compartments on mortality. Intra-abdominal fat was related to cardiovascular disease mortality, whereas lower muscle mass and lower subcutaneous fat increased cancer mortality, independently of smoking. Fat distribution may explain the differential associations observed for CVD with BMI on the one hand, and with central adiposity markers (WHR or WC) on the other side. As such, an increased WHR/WC may reflect a larger intra-abdominal fat mass or a decreased gluteo-femoral muscle mass - two body compartments that are not well captured by using BMI alone.

Conclusions

In this individual-participant data meta-analysis of 82,864 individuals from 9 nationwide British cohorts, we found that greater WC and WHR were associated with an increased risk for CVD and all-cause mortality, with WHR showing the highest magnitude of association. In multivariate models, global adiposity assessed by BMI was not associated with CVD risk and was inversely related to all-cause mortality risk. No clinically relevant difference in discrimination capabilities was observed between these three adiposity variables.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Derivation of the analytic sample
HSE: Health Survey for England, SHS: Scottish Health Survey

Figure 2. Age and sex-adjusted associations between anthropometric variables and mortality
Upper row of figures is for all-cause mortality, lower for CVD mortality

For the association between each anthropometric variable and the outcome of interest, boxes are for the effect estimate (hazard ratio) and the vertical bars about are for the 95% confidence interval (CI). On the horizontal axis, the hazard ratio for each quintile is plotted against the quintile specific median of the anthropometric variable. For each figure, the hazard ratio (HR) and the 95% CI for a standard deviation for a one higher standard deviation in each anthropometric variables are shown. The p-value is for the log-linearity of the association. The vertical axis is on log scale to allow equal distribution of the CI about the estimates.

Figure 3. Multivariable adjusted associations between anthropometric variables and mortality
 Conventions are as per figure 2. Covariates in the models are age, sex, cohorts, diabetes status, systolic blood pressure, history of CVD, social class, physical activity, smoking status, total cholesterol

Table 1
Characteristics of each study contributing to present individual-participant meta-analysis

Cohort	Year of survey	Total participants, n	Included study members , %	Characteristics of included study members			
				women, n	Age, y *	Total death, n	CVD death, n
HSE	1994	10599	81.7	4667	55.4 (14.0)	1854	375
HSE	1997	5875	79.4	2474	54.7 (13.3)	651	204
HSE	1998	11058	76.7	4589	55.2 (13.7)	1090	381
HSE	2001	11283	68.1	4119	54.9 (13.3)	503	177
HSE	2002	5399	68.7	2055	54.7 (13.7)	199	81
HSE	2003	10887	66.3	3905	55.2 (13.3)	286	104
SHS	1995	4525	73.0	1804	49.3 (8.9)	444	124
SHS	1998	11636	66.4	4260	50.1 (11.6)	1196	388
SHS	2003	11602	50.9	3226	57.2 (13.4)	418	164

HSE: Health Survey for England; SHS: Scottish Health Survey;

*
 mean±SD

“Included study members” are those who consented to follow-up and had data on body mass index, BMI; waist circumference, WC and waist-to-hip ratio, WHR.

Table 2
Baseline characteristics of participants according to inclusion in the present analysis

Variables	Included study members		Excluded study members		P value for difference
	N	Mean (SD)	N	Mean (SD)	
N		57356		25508	
Age (years)	57356	54.8 (13.2)	25508	56.3 (14.8)	<0.0001
Men (%)	57356	45.8	25508	42.1	<0.0001
Systolic blood pressure (mmHg)	55831	136.0 (20.1)	10690	136.2 (20.3)	0.27
Total cholesterol (mg/dl)	32772	5.9 (1.2)	6319	5.8 (1.2)	<0.0001
HDL-cholesterol (mg/dl)	22316	1.49 (0.42)	5211	1.48 (0.41)	0.37
BMI (kg/m ²)	57356	27.3 (4.8)	49840	27.4 (5.1)	0.0001
WC (cm)	57356	91.3 (13.2)	49840	92.3 (14.4)	0.007
WHR	57356	0.87 (0.09)	10153	0.87 (0.09)	0.003
History of CVD *	41285	4219 (10.2)	19007	2010 (10.6)	0.18
History of diabetes *	41283	1650 (4)	19008	1040 (4.6)	0.0009
History of hypertension *	41127	10608 (25.8)	18942	5101 (26.9)	0.003
Smoking *	57251	13972 (24.4)	25347	6445 (25.4)	0.002

BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; CVD, cardiovascular disease.

* Results are N (%)

“Included study members” were study members who gave consent for follow-up and had full data for BMI, WC and WHR.

“Excluded study members” were study members who did not give consent for follow-up or who had missing data for BMI, or WC or WHR.

Table 3
Hazard ratios (95% confidence intervals) for the association between conventional risk factors and mortality outcomes

	All death	CVD death
Age (per one SD increase)	3.84 (3.72-3.95)	4.79 (4.52-5.08)
Sex (women vs. men)	0.64 (0.61-0.67)	0.56 (0.52-0.62)
Systolic blood pressure (per one SD increase)	1.03 (1.01-1.06)	1.09 (1.04-1.14)
History of diabetes (yes vs. no)	1.79 (1.62-1.97)	2.27 (1.94 –2.66)
Total cholesterol (per one SD increase)	0.92 (0.89-0.95)	0.99 (0.93-1.05)
HDL-cholesterol (per one SD increase)	0.94 (0.90-0.99)	0.77 (0.71-0.84)
History of cardiovascular disease (yes vs. no)	1.65 (1.55-1.76)	2.44 (2.20-2.72)
Smoking (yes vs. no)	2.17 (2.06-2.30)	2.14 (1.93-2.37)
Socioeconomic status (Non-manual occupation [high] vs. manual [low])	0.54 (0.47-0.62)	0.39 (0.29-0.52)

Hazard ratios are adjusted for age, sex and cohort except age (sex and cohort adjusted) and sex (age and cohort adjusted). CVD, cardiovascular disease

Table 4
Area under the receiver operating characteristic curves (95% confidence intervals) for
the prediction of total and cardiovascular disease mortality

Model	Total death	CVD death
BMI (A)	0.847 (0.840-0.855)	0.868 (0.856-0.880)
WC (B)	0.847 (0.839-0.855)	0.868 (0.856-0.880)
WHR (C)	0.848 (0.840-0.856)	0.868 (0.856-0.880)
P for the difference in AUC		
A-B	0.03	0.86
A-C	0.22	0.80
B-C	<0.0001	0.68

BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; CVD, cardiovascular disease.

Multivariate models are adjusted for: cohorts, age, sex, diabetes status, systolic blood pressure, history of CVD, social class, physical activity, smoking status and total cholesterol

Table 5
Relative integrated discrimination improvement statistics (RIDI, 95% confidence intervals) comparing models with a given anthropometric variable with models for which the variable has been replaced by another anthropometric variable

Model 1	Model 2	All death	CVD death
BMI	WC	0.150 (0.140-0.160)	0.543 (0.524-0.563)
BMI	WHR	0.335 (0.321-0.348)	0.265 (0.236-0.295)
WC	WHR	0.184 (0.175-0.193)	-0.276 (-0.302 to -0.250)

BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; CVD, cardiovascular disease.

Multivariate models are adjusted for: cohorts, age, sex, diabetes status, systolic blood pressure, history of CVD, social class, physical activity, smoking status and total cholesterol