OPEN ACCESS

Check for updates

Central fatness and risk of all cause mortality: systematic review and dose-response meta-analysis of 72 prospective cohort studies

Ahmad Jayedi,[1,2] Sepideh Soltani,[3,4] Mahdieh Sadat Zargar,[5] Tauseef Ahmad Khan,[6,7,8] Sakineh Shab-Bidar[2]

For numbered affiliations see end of the article.

Correspondence to: S Shab-Bidar s_shabbidar@tums.ac.ir (ORCID 0000-0002-0167-7174)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2020;370:m3324

http://dx.doi.org/10.1136/bmj.m3324

Accepted: 11 August 2020

ABSTRACT

OBJECTIVE

To quantify the association of indices of central obesity, including waist circumference, hip circumference, thigh circumference, waist-to-hip ratio, waist-to-height ratio, waist-to-thigh ratio, body adiposity index, and A body shape index, with the risk of all cause mortality in the general population, and to clarify the shape of the dose-response relations.

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

PubMed and Scopus from inception to July 2019, and the reference lists of all related articles and reviews.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Prospective cohort studies reporting the risk estimates of all cause mortality across at least three categories of indices of central fatness. Studies that reported continuous estimation of the associations were also included.

DATA SYNTHESIS

A random effects dose-response meta-analysis was conducted to assess linear trend estimations. A one stage linear mixed effects meta-analysis was used for estimating dose-response curves.

RESULTS

Of 98 745 studies screened, 1950 full texts were fully reviewed for eligibility. The final analyses consisted of 72 prospective cohort studies with 2 528 297 participants. The summary hazard ratios were as follows: waist circumference (10 cm, 3.94 inch increase): 1.11 (95% confidence interval 1.08 to 1.13, I^2=88%, n=50); hip circumference (10 cm, 3.94 inch increase): 0.90 (0.81 to 0.99, I^2=95%, n=9); thigh circumference (5 cm, 1.97 inch increase): 0.82 (0.75 to 0.89, I^2=54%, n=3); waist-to-hip ratio (0.1 unit increase): 1.20 (1.15 to 1.25, I^2=90%, n=31); waist-to-height ratio (0.1 unit increase): 1.24 (1.12 to 1.36, I^2=94%, n=11); waist-to-thigh ratio (0.1 unit increase): 1.21 (1.03 to 1.39, I^2=97%, n=2); body adiposity index (10% increase): 1.17 (1.00 to 1.33, I^2=75%, n=4); and A body shape index (0.005 unit increase): 1.15 (1.10 to 1.20, I^2=87%, n=9). Positive associations persisted after accounting for body mass index. A nearly J shaped association was found between waist circumference and waist-to-height ratio and the risk of all cause mortality in men and women. A positive monotonic association was observed for waist-to-hip ratio and A body shape index. The association was U shaped for body adiposity index.

CONCLUSIONS

Indices of central fatness including waist circumference, waist-to-hip ratio, waist-to-height ratio, waist-to-thigh ratio, body adiposity index, and A body shape index, independent of overall adiposity, were positively and significantly associated with a higher all cause mortality risk. Larger hip circumference and thigh circumference were associated with a lower risk. The results suggest that measures of central adiposity could be used with body mass index as a supplementary approach to determine the risk of premature death.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Existing evidence suggests that central fatness might be more strongly associated with the risk of mortality than overall obesity, however the results have not been quantitatively gathered

Several large scale prospective cohort studies have suggested a positive linear or J shaped association between indices of central fatness with all cause mortality risk

Systematic reviews and meta-analyses assessing the dose-response association between indices of central fatness and all cause mortality risk are lacking

WHAT THIS STUDY ADDS

Central fatness, reflected by large waist circumference, waist-to-hip ratio, and waist-to-height ratio, independent of overall adiposity, was associated with a higher risk of all cause mortality

The results suggest a nearly J shaped association between waist circumference and risk of all cause mortality

Larger hip circumference and thigh circumference were associated with a lower risk of all cause mortality

Introduction

Two recent comprehensive meta-analyses assessed the association of general adiposity, represented by body mass index, with the risk of all cause mortality in the general population.[1 2] The authors included more than 200 prospective cohort studies and the results indicated that a U shaped and a J shaped association existed between body mass index and the risk of all cause mortality in the general population and healthy never smokers, respectively. The lowest risk was observed for a body mass index of 22-23 in healthy never smokers. Body mass index is easy to obtain and so is the most frequent anthropometric measure used to investigate obesity-mortality and obesity-morbidity associations.

The validity of body mass index as an appropriate indicator of obesity has been questioned.[3] Research suggests that body mass index does not differentiate

between lean body mass and fat mass; therefore, when using body mass index as a measure, inaccurate assessment of adiposity could occur.[4] Additionally, the most important limitation of body mass index is that it does not reflect regional body fat distribution. Existing evidence suggests that central obesity and abdominal deposition of fat is more strongly associated with cardiometabolic risk factors[5 6] and chronic disease risk[7-10] than overall obesity. Furthermore, most studies, especially large scale cohort studies, that have assessed the association of body mass index with the risk of mortality have used self-report height and weight to calculate body mass index.[1] Participants tend to under report their weight and over report their height, which could result in inaccurate assessment of adiposity.[11] In contrast, most studies assessing the association of central fatness with the risk of chronic disease used measured anthropometry.

Taking this evidence into account, indices of central obesity might be more accurate than body mass index when estimating adiposity, and therefore could be more closely and strongly associated with the risk of mortality. Despite the evidence, systematic reviews and meta-analyses are lacking that comprehensively assess the association of indices of central fatness with the risk of all cause mortality in the general population. Only a few meta-analyses of prospective cohort studies have assessed the association of indices of central adiposity with all cause mortality risk[12-14]; however, they have important limitations. For example, they were performed in older populations,[13] they did not perform non-linear dose-response analyses,[14] or they did not include most of the evidence.[12] Another pooled analysis of 11 prospective cohort studies assessed the association of waist circumference with the risk of all cause mortality,[15] but they only included studies from Western countries.

We aimed to perform a systematic review and dose-response meta-analysis of prospective cohort studies to investigate the association of indices of central fatness with the risk of all cause mortality in the general population, in never smokers, and in healthy never smokers. The indices of central fatness were waist circumference, hip circumference, thigh circumference, waist-to-hip ratio, waist-to-height ratio, waist-to-thigh ratio, body adiposity index, and A body shape index. Whenever possible, we clarified the shape of the dose-response relations. Additionally, we performed a meta-analysis to compare the risk of all cause mortality associated with a one standard deviation increment across different measures of central fatness.

Methods

We used the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement as guidance for reporting this systematic review.[16] We also followed the 12 item PRISMA extension when writing the abstract.[17]

Search strategy

We combined keywords relevant to general and central obesity, mortality, and study design to find potentially relevant studies (table S1 in appendix 1). We searched PubMed and Scopus databases from inception to July 2019, followed by a hand search of the reference lists of related articles and reviews. We restricted our systematic search to articles published in English.

Eligibility and study selection

Two authors (AJ and MSZ) reviewed the title and abstract of all articles obtained. They selected potentially eligible studies that were conducted in the general population (aged >18 years and older); had a prospective observational design; considered self-reported or measured anthropometric indices as exposure and in at least three quantitative categories; considered all cause mortality as the outcome of interest; reported adjusted effect sizes across categories of exposures; and provided the numbers of participants or person years and events across categories of exposures. All cause mortality was defined as death by any cause, including non-communicable diseases such as cardiovascular disease, site specific cancers, type 2 diabetes, and respiratory disease, communicable and infectious diseases, and any other cause of death.

We also included studies that reported continuous estimation of the associations. For duplicate publications, those with the largest number of participants were included. However, when different publications from the same study reported effect sizes as categorical and continuous, the study with the categorical model was selected for inclusion in both linear and non-linear dose-response analyses. Some study publications reported effect sizes as categorical but the exact amount of the standard deviation was not reported in the text, while other publications from the same study reported the direct effect size for a one standard deviation increment in anthropometric measures. For these studies, the publication with the categorical model was included in dose-response analyses and another publication that reported the direct effect size for a one standard deviation increment was included in the standard deviation analysis. We excluded retrospective studies, studies in populations with diseases, studies of older people living in institutions, and studies with populations aged 85 years and older.

Data extraction and assessment for study quality

One author (MSZ) extracted data from each primary prospective cohort study by using prespecified data extraction forms. The first author (AJ) checked the data extracted from each study to ensure that all data were extracted correctly. The information extracted from eligible studies was the first author's name, publication year, study name, location, age range or mean age (years), sex, number of participants, follow-up duration, anthropometric assessment method, and confounding factors in the multivariable analysis. All meta-analyses were conducted by using the maximally adjusted effect sizes reported in primary studies.

doi: 10.1136/bmj.m3324 | BMJ 2020;370:m3324 | the bmj

However, for studies that controlled for intermediate variables, such as blood pressure or hypertension, lipid profile, and diabetes in their maximally adjusted model, the alternative model without these intermediate variables was selected and included in the meta-analyses.[1 15] If the alternative model was age adjusted only, the multivariable model covering intermediate variables was selected. When studies reported effect sizes with and without controlling for body mass index, we included the model with adjustment for body mass index in the main analyses. However, we performed subgroup analyses on the basis of adjustment for body mass index. When studies had insufficient data, we contacted the authors twice, with a two week interval, but only one study author provided the requested data. We used the Newcastle-Ottawa scale to assess the quality of the studies included in the meta-analyses.[18] Any discrepancies were resolved through discussion to reach consensus.

Data synthesis and statistical analysis

We performed random effects meta-analyses[19] to calculate summary hazard ratios and 95% confidence intervals for a 10 cm (3.94 inch) increment in waist circumference and hip circumference; a 5 cm (1.97 inch) increase in thigh circumference; a 0.1 unit increment in waist-to-hip ratio, waist-to-thigh ratio, and waist-to-height ratio; a 10% increment in body adiposity index; and a 0.005 unit increment in A body shape index. The reported relative risks were considered equal to hazard ratios.[20] We used the generalised least squares trend estimation method, introduced by Greenland and colleagues,[21 22] to measure the linear dose-response relations. This method needs distribution of events and participants or person years and adjusted risk estimates across categories of anthropometric measures. The median point in each category was assigned to the corresponding hazard ratio. When studies did not report the direct median of each category, we estimated approximate medians by using the midpoint of the lower and upper bounds. We assumed that open ended categories had the same interval as the adjunct category. For studies that did not report the numbers of participants or person years in each category, we estimated these values by dividing the total number of participants or person years by the number of categories if the exposures were defined as quantiles.[23 24] When studies reported separate effect sizes across sex or other subgroups, we pooled the subgroup specific estimates by using a fixed effects model and used the pooled effect size for meta-analysis. For studies that did not consider the lowest category as the reference, we excluded the categories below the reference category to measure the linear dose-response relations.[1]

Two studies reported continuous estimation of the associations, but the hazard ratios and 95% confidence intervals across categories of exposures were shown in figures only. Therefore, we estimated hazard ratios and 95% confidence intervals by using a web plot digitiser.[25] We tested the accuracy of the results by calculating hazard ratios and 95% confidence intervals for a one standard deviation increment in exposures. We used data obtained by software and compared them with the direct continuous estimation reported in the text, which indicated close results (hazard ratio 1.22 obtained by estimation compared with 1.24 reported in the text). We evaluated the potential influence of each study on the summary hazard ratios by re-estimating the hazard ratios after excluding one study at a time. We performed subgroup analyses by sex, geographical location, anthropometric assessment method, follow-up duration, number of participants, study quality, adjustment for main confounders (physical activity, smoking, body mass index, and alcohol intake) and intermediates (blood pressure, serum cholesterol, and type 2 diabetes). We controlled for smoking status and pre-existing diseases by performing additional sensitivity analyses. Analyses were restricted to never smokers, healthy participants, and healthy never smokers, whenever possible. Analyses of healthy participants included studies that excluded participants with a history of cancer and cardiovascular disease at baseline. We evaluated between study heterogeneity by using the I^2 statistic and Cochran's Q test of heterogeneity.[26] Publication bias was assessed with Egger's asymmetry test[27] and Begg's test[28] if sufficient studies existed (n≥10).[29]

We also tested for a non-linear dose-response association. We modelled the exposures by using restricted cubic splines with three knots according to Harrell's recommended percentiles (10%, 50%, and 90%)[30] of the distribution. The correlation within each category of published hazard ratios was taken into account and the study specific estimates were combined by using a one stage linear mixed effects meta-analysis.[31] This method estimates the study specific slope lines and combines them to obtain an overall average slope[32 33] in a single stage, and is a more precise, flexible, and efficient method than the traditional two stage method.[31]

Some studies did not consider the lowest category as the reference, therefore we recalculated effect sizes by assuming the lowest category as the reference[34]; all categories of exposure in the non-linear dose-response meta-analyses were included and the associations across the entire exposure ranges were modelled.[1] Similar to the linear trend estimation, we performed sensitivity analyses by restricting the analyses to never smokers, healthy never smokers, and to studies that controlled for body mass index in their multivariable analyses. Additionally, we performed separate non-linear dose-response analyses on the basis of follow-up duration to better control for pre-existing diseases. Participants with pre-existing diseases are more likely to experience death in the early years of follow-up, and so the proportion of deaths caused by pre-existing diseases, and the confounding effects of pre-existing diseases, decline with the increase in follow-up duration. Therefore, studies with long term follow-up durations might present a more accurate estimation of the associations.

We compared the associations across different measures of central obesity by conducting an additional analysis to quantify the associations for a one standard deviation increment in anthropometric measures. We estimated hazard ratios for a one standard deviation increment in measures in each study, and then pooled hazard ratios by using a random effects model. When studies reported direct effect sizes for a one standard deviation increment in exposures, we included the hazard ratios in the meta-analysis as reported. For studies that reported the hazard ratio per specific amount of increase in anthropometric measures, we exponentiated the log (hazard ratio) times the study specific standard deviation of the anthropometric measure to obtain the hazard ratio for an increment of one standard deviation in the level of the anthropometric measures. When studies grouped the exposure in quantiles, we estimated the hazard ratios for a one standard deviation increment by using the methods developed by Greenland and colleagues.[21] All analyses were conducted with Stata software, version 15 (Stata Corp, College Station, TX).

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There was a meta-analysis skill level that could not be easily learned by a member of the public with basic research training.

Results

We found 110 199 publications through database searching plus four publications through hand searching, of which 11 458 records were duplicates. We reviewed titles and abstracts of all remaining publications and another 96 795 publications were excluded, yielding 1950 studies for full text assessment (fig S1 in appendix 1). Of these studies, 70 publications provided sufficient information for the meta-analysis. Two publications reported the results of the two separate cohort studies and were regarded as two separate studies.[35 36] Ultimately, 72 prospective cohort studies with 2 528 297 participants and 150 164 events were included in final analyses.[35-104] Thirty studies were from Europe, 22 studies were from the United States, 16 studies were from Asia, two studies were from Canada, one from Brazil, and one from Tobago in South America. Twelve studies included only men, 12 studies included only women, and another 48 studies included both sexes. Follow-up durations were between 3 and 24 years. Seven studies used self-reported anthropometric measures and 65 studies measured anthropometric indices.

Three different publications from the third National Health and Nutrition Examination Survey were included in the analyses of waist-to-height ratio,[59] thigh circumference,[102] and waist circumference, waist-to-hip ratio, and waist-to-thigh ratio.[86] Another publication from this study that reported direct estimations for one standard deviation increment in anthropometric measures was included in the analyses of standard deviations.[63] Four different publications from the Danish MONICA study were included in the analyses of hip circumference (women only),[71] hip circumference (men only),[57] thigh circumference,[56] and waist circumference.[66] Two separate publications from the Danish diet, cancer and health study were included in the analyses of waist circumference[41] and hip circumference.[42] Fifty studies were included in the analysis of waist circumference, nine studies in the analysis of hip circumference, and three in the analysis of thigh circumference; 31, 11, 2, 4, and 9 studies were included in the analyses of waist-to-hip ratio, waist-to-height ratio, waist-to-thigh ratio, body adiposity index, and A body shape index, respectively.

We summarise general characteristics of the studies included in the present meta-analysis in table S2 (appendix 1). Table S3 (appendix 1) presents the reported effect sizes across categories of each exposure in the primary studies, and table S4 gives the qualities of studies assessed by the Newcastle-Ottawa scale.

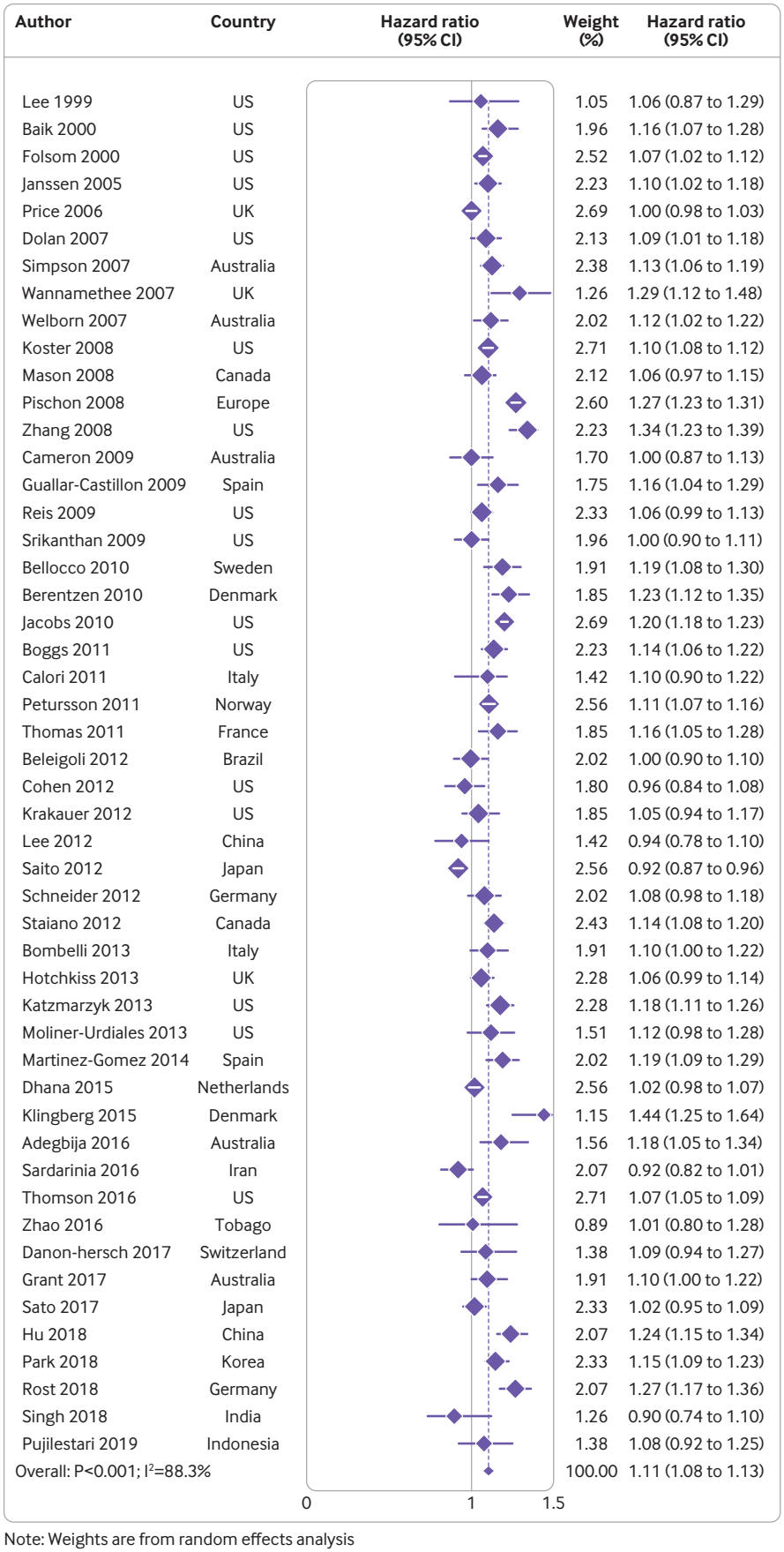
Waist circumference

The systematic search identified 50 eligible cohort studies with 128 842 all cause mortality events among 2 056 428 participants for the relation of waist circumference and the risk of all cause mortality.[37-44 46-54 58 60-62 65-68 73 74 77 78 80-97 100 101 103 104] The pooled analysis indicated that each 10 cm (3.94 inch) increment in waist circumference was associated with an 11% higher risk of all cause mortality: hazard ratio 1.11 (95% confidence interval 1.08 to 1.13), with high heterogeneity (I^2=88%, $P_{heterogeneity}$<0.001; fig 1, table 1). The summary hazard ratio remained unchanged when each study was sequentially removed from the main analysis. The hazard ratios were 1.08 (1.04 to 1.13; I^2=87%, n=27) and 1.12 (1.09 to 1.16, I^2=85%, n=30) in men and women, respectively.

In the subgroup analyses, a trend was found towards a higher risk with increasing follow-up duration and number of events (table 1). The association was significant when we controlled for smoking status, physical activity, and alcohol consumption, and strengthened when we controlled for body mass index: hazard ratio 1.17 (1.13 to 1.22, I^2=86%, n=15). The association was not significant in participants older than 60 years: hazard ratio 1.03 (0.98 to 1.08, I^2=81%, n=14). Follow-up duration, study quality, and adjustment for smoking could be sources of heterogeneity. No evidence was found of publication bias with Egger's test (P=1.00) and Begg's test (P=0.58; fig S2 in appendix 1).

Fourteen studies with 45 783 events among 731 954 healthy participants[28 38 40 52 61 62 65 66 67 82 83 90 97 103] reported sufficient data for the analyses of healthy participants. Eight studies with 27 377 events among 285 874 never smokers[39 43 51 67 92 97 99 103] and five studies with 26 210 events among 276 409 healthy

doi: 10.1136/bmj.m3324 | BMJ 2020;370:m3324 | the bmj



Note: Weights are from random effects analysis

Fig 1 | Summary hazard ratio of all cause mortality for a 10 cm increment in waist circumference

Table 1 | Subgroup analyses of waist circumference (10 cm increase) and risk of all cause mortality

Characteristics	n	Hazard ratio (95% CI)	I^2 (%), $P_{hetrogeneity}$
All studies	50	1.11 (1.08 to 1.13)	88, <0.001
Sex			
Men	27	1.08 (1.04 to 1.13)	87, <0.001
Women	30	1.12 (1.09 to 1.16)	85, <0.001
Healthy participants			
All	14	1.15 (1.10 to 1.20)	91, <0.001
Men	8	1.16 (1.07 to 1.24)	91, <0.001
Women	12	1.13 (1.09 to 1.18)	87, <0.001
Never smokers			
All	8	1.10 (1.05 to 1.14)	68, 0.003
Men	3	1.06 (0.94 to 1.18)	52, 0.13
Women	6	1.12 (1.07 to 1.17)	67, 0.009
Healthy never smokers			
All	5	1.12 (1.07 to 1.17)	71, 0.008
Men	2	1.04 (0.93 to 1.16)	64, 0.10
Women	5	1.13 (1.09 to 1.18)	50, 0.09
Geographical region			
US	18	1.11 (1.08 to 1.15)	86, <0.001
Europe	17	1.15 (1.09 to 1.21)	91, <0.001
Asia	13	1.06 (1.01 to 1.12)	85, <0.001
South America	2	1.00 (0.91 to 1.09)	0, 0.94
Follow-up duration (years)			
<5	7	1.06 (0.99 to 1.12)	63, <0.001
5-10	25	1.13 (1.08 to 1.17)	90, <0.001
10-15	14	1.07 (1.04 to 1.11)	78, <0.001
15-20	3	1.28 (1.20 to 1.36)	48, 0.14
>20	1	1.02 (0.98 to 1.07)	—
Anthropometric assessment			
Measured	44	1.10 (1.07 to 1.13)	86, <0.001
Self-reported	6	1.17 (1.10 to 1.23)	92, <0.001
No of events			
<500	16	1.05 (1.00 to 1.10)	56, 0.003
500-1000	13	1.13 (1.09 to 1.18)	60, <0.001
1000-2000	7	1.08 (1.00 to 1.16)	88, 0.002
>2000	14	1.14 (1.09 to 1.18)	88, >0.001
Population body mass index			
<25	4	1.19 (1.00 to 1.37)	92, <0.001
≥25	4	1.33 (1.17 to 1.49)	84, <0.001
Study quality (stars)			
0–3	-	-	-
4–6	5	1.03 (0.99 to 1.08)	7, 0.37
7–9	45	1.12 (1.09 to 1.15)	89, <0.001
Adjustment for confounders			
Body mass index			
Yes	15	1.17 (1.13 to 1.22)	86, <0.001
No	35	1.08 (1.05 to 1.10)	78, <0.001
Physical activity			
Yes	29	1.16 (1.13 to 1.19)	86, <0.001
No	21	1.04 (1.00 to 1.07)	67, <0.001
Smoking status			
Yes	43	1.11 (1.08 to 1.14)	90, <0.001
No	7	1.09 (1.06 to 1.12)	0, 0.90
Alcohol drinking			
Yes	31	1.13 (1.10 to 1.17)	92, <0.001
No	19	1.06 (1.03 to 1.09)	57, 0.001
Body mass index, physical activity, smoking status, and alcohol drinking			
Yes	11	1.19 (1.14 to 1.24)	90, <0.001
No	39	1.08 (1.05 to 1.11)	77, <0.001
Adjustment for intermediates			
Blood pressure			
Yes	10	1.08 (1.02 to 1.13)	75, <0.001
No	40	1.11 (1.08 to 1.15)	90, <0.001
Serum cholesterol			
Yes	9	1.06 (1.01 to 1.10)	87, 0.002
No	41	1.12 (1.09 to 1.15)	89, <0.001
Type 2 diabetes			
Yes	7	1.07 (1.01 to 1.14)	77, <0.001
No	43	1.11 (1.08 to 1.14)	89, <0.001
Blood pressure, serum cholesterol, and type 2 diabetes			
Yes	6	1.06 (0.99 to 1.13)	77, 0.001
No	44	1.11 (1.08 to 1.14)	89, <0.001

doi: 10.1136/bmj.m3324 | *BMJ* 2020;370:m3324 | the bmj

never smokers[43 67 92 97 103] also reported sufficient data for the analyses of never smokers and healthy never smokers, respectively. Changes were weak in comparison to the main analysis, expect for men in whom the associations became non-significant in never smokers and healthy never smokers (table 1).

Thirty two studies reported sufficient data for the non-linear dose-response analyses.[37 38 40 43 47- 49 52-54 58 60 61 66-68 73 74 81-84 86-88 91 92 96 97 99 100 103] The analysis of women indicated a J shaped association. The risk of all cause mortality did not change for a waist circumference of 60-80 cm (hazard ratio$_{80cm}$ 1.01, 95% confidence interval 0.99 to 1.03) and then increased sharply and linearly ($P_{non\text{-}linearity}$<0.001, n=23; fig 2). The results for healthy women ($P_{non\text{-}linearity}$<0.001, n=10), studies that controlled for body mass index ($P_{non\text{-}linearity}$=0.002, n=7), studies with more than 10 years of follow-up ($P_{non\text{-}linearity}$<0.001, n=10), women who were never smokers ($P_{non\text{-}linearity}$<0.001, n=6), and healthy women who were never smokers ($P_{non\text{-}linearity}$<0.001, n=5) are presented in figure 2. The results for men are presented in figure 3. The analysis of men indicated a J shaped relation with the risk of all cause mortality, which was lowest at a waist circumference of 90 cm (hazard ratio$_{90cm}$ 0.96, 95% confidence interval 0.94 to 0.98), and then increased sharply and linearly ($P_{non\text{-}linearity}$<0.001, n=16; fig 3).

Waist-to-hip ratio

Thirty one cohort studies (30 publications) with 1 112 816 participants and 75 183 all cause mortality events were considered eligible for the analysis of waist-to-hip ratio and the risk of all cause mortality.[35 38 45 47 48 50 52 58 64 65 70 72 74 75 78 82 83 84 86 87 89 91 92 94 95 97 98 100 101 103] Every 0.1 unit increment in waist-to-hip ratio was associated with a 20% higher risk: hazard ratio 1.20 (95% confidence interval 1.15 to 1.25, I^2=90%, n=31; fig 4). The hazard ratio did not change when we excluded each study one at a time. The association was stronger in women than in men (1.121 *v* 1.16), and became stronger with increasing follow-up duration and number of events (table 2). A significant

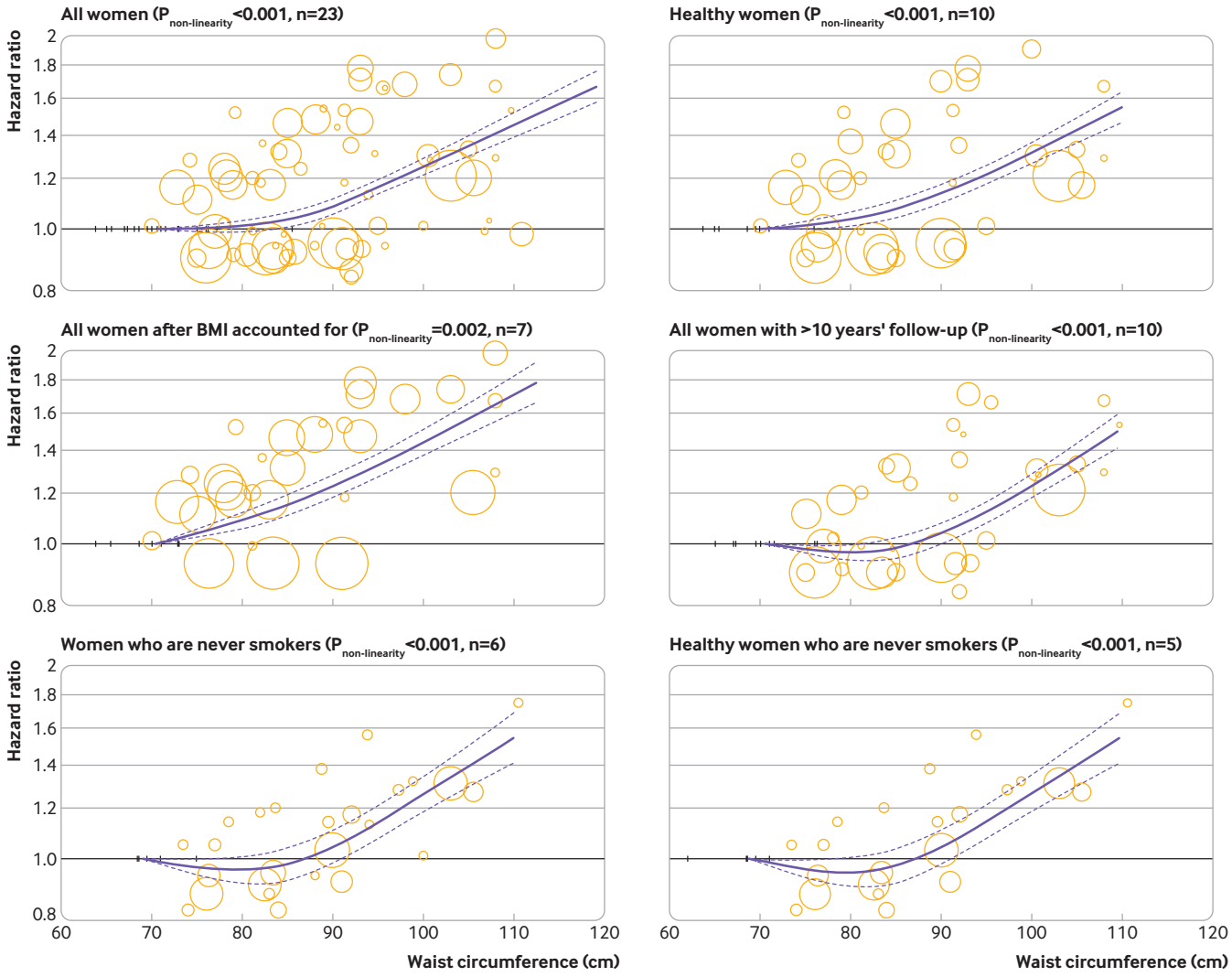


Fig 2 | Dose-response association of waist circumference with risk of all cause mortality in women. Solid line represents non-linear dose response and dotted lines represent 95% confidence interval. Circles represent hazard ratio point estimates for adiposity categories from each study with circle size proportional to inverse of standard error. Small vertical black lines represent baseline adiposity category for each separate study

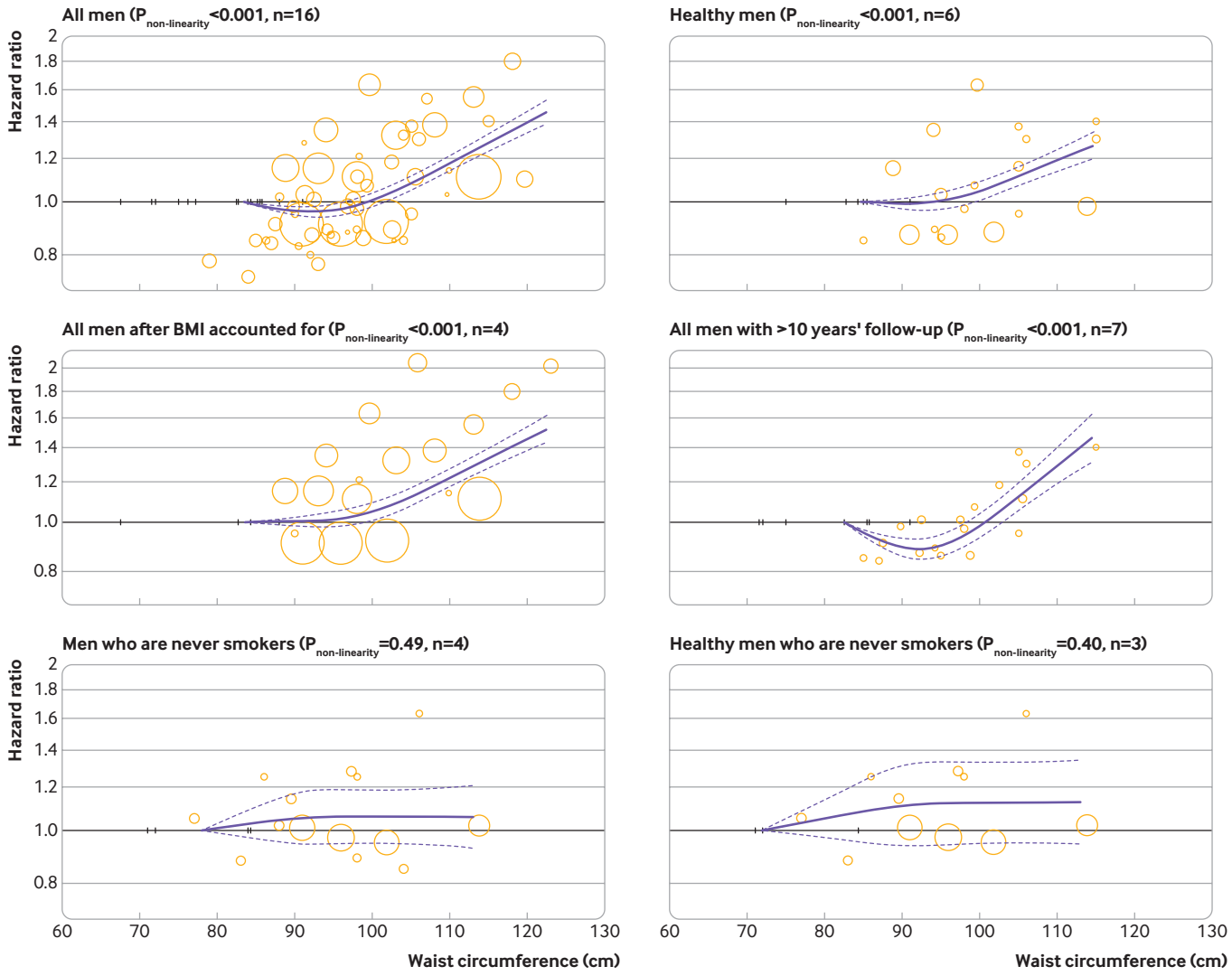


Fig 3 | Dose-response association of waist circumference with risk of all cause mortality in men. Solid line represents non-linear dose response and dotted lines represent 95% confidence interval. Circles represent hazard ratio point estimates for adiposity categories from each study with circle size proportional to inverse of standard error. Small vertical black lines represent baseline adiposity category for each separate study

association remained stable among studies that adjusted for physical activity, alcohol consumption, smoking status, and body mass index. The association became weaker in participants older than 60 years: hazard ratio 1.09 (1.01 to 1.17, I^2=76%, n=8). The subgroup analyses suggested that follow-up duration, number of events, study quality, and anthropometric assessment method were potential sources of between study heterogeneity. No evidence of publication bias was observed with Egger's test (P=0.19) and Begg's test (P=0.52; fig S3 in appendix 1).

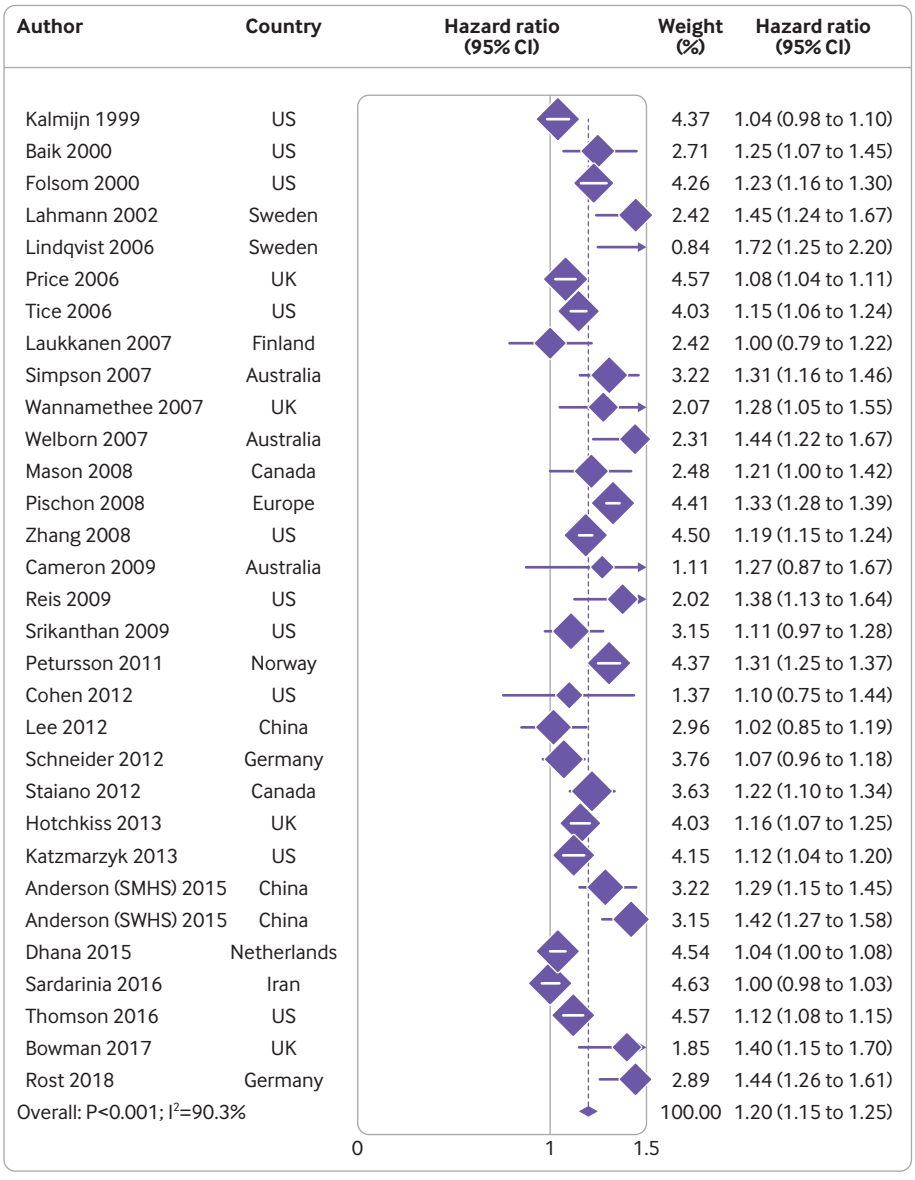
Nine cohort studies with 516 998 healthy participants and 26 285 events[38 45 52 65 72 82 83 97 103] reported sufficient data for the analyses of healthy participants. Eight studies (seven publications) with 17 107 events among 304 443 never smokers[35 45 65 92 97 99 103] and three studies with 11 535 events among 203 758 healthy never smokers[45 97 103] also reported sufficient data for the analyses of never smokers and healthy never smokers, respectively. The associations remained unchanged in healthy participants, but attenuated weakly in never smokers (table 2).

Twenty two cohort studies (21 publications) reported sufficient data for the non-linear dose-response meta-analyses.[35 45 47 48 52 58 64 70 74 82-84 86 87 91 92 97-100 103] Figure 5 presents the results for all participants ($P_{non-linearity}$<0.001, n=22), all participants after body mass index was accounted for ($P_{non-linearity}$=0.06, n=7), healthy participants ($P_{non-linearity}$<0.001, n=6), and never smokers ($P_{non-linearity}$=0.42, n=5). Overall the relations were monotonic with little evidence of sharp changes at particular cut-off points (fig 5). Additionally, we performed separate analyses for men ($P_{non-linearity}$<0.001, n=15) and women ($P_{non-linearity}$=0.41, n=18), which showed similar monotonic relations.

Waist-to-height ratio

Eleven studies with 760 190 participants and 23 959 events of all cause mortality were included in the analysis of waist-to-height ratio.[50 59 60 65 81 82 87 89-91 101]

doi: 10.1136/bmj.m3324 | *BMJ* 2020;370:m3324 | the bmj



Note: Weights are from random effects analysis

Fig 4 | Summary hazard ratio of all cause mortality for 0.1 unit increment in waist-to-hip ratio. SMHS=Shanghai men's health study; SWHS=Shanghai women's health study

The summary hazard ratio for a 0.1 unit increment in waist-to-height ratio was 1.24 (95% confidence interval 1.12 to 1.36, I^2=94%; fig 6, table 3). Exclusion of each study one at a time did not materially alter the results (hazard ratio range 1.21-1.27). The hazard ratios were 1.13 (1.01 to 1.24, I^2=77%, n=8), 1.20 (1.07 to 1.32, I^2=89%, n=8), and 1.18 (1.03 to 1.34, I^2=88%, n=4) in men, women, and healthy participants, respectively.[65 82 90 91] The hazard ratio was 1.42 (1.16 to 1.69, I^2=69%, n=2) in studies that controlled for body mass index. Table S5 (appendix 1) presents the results for subgroup analyses. Adjustment for body mass index, alcohol intake, and geographical region were potential sources of heterogeneity. Publication bias tests showed some evidence of bias with Egger's test (P=0.05) and Begg's test (P=0.08; fig S4 in appendix 1).

Five studies were eligible for the non-linear dose-response analysis.[60 81 82 87 91] The analyses showed significant dose dependent relations between waist-to-height ratio and mortality risk in the analyses of all participants ($P_{non\text{-}linearity}$<0.001, n=5) and healthy participants ($P_{non\text{-}linearity}$=0.005, n=2 studies with sex specific effect sizes; fig 7). Both men ($P_{non\text{-}linearity}$=0.05, n=3) and women ($P_{non\text{-}linearity}$=0.001, n=3) showed a similar J shaped non-linear response (fig 7). The all cause mortality risk was lowest at 0.50 (men: hazard $ratio_{0.50unit}$ 0.96, 0.94 to 0.98; women: hazard $ratio_{0.50unit}$ 0.90, 0.78 to 1.05), after which a sharp linear increase was observed.

Table 2 | Subgroup analyses of waist-to-hip ratio (0.1 unit increase) and risk of all cause mortality

Characteristics	n	Hazard ratio (95%CI)	I^2 (%), $P_{hetrogeneity}$
All studies	31	1.20 (1.15 to 1.25)	90, <0.001
Sex			
Men	21	1.16 (1.09 to 1.23)	88, <0.001
Women	23	1.21 (1.16 to 1.26)	84, <0.001
Healthy participants			
All	9	1.21 (1.15 to 1.28)	88, <0.001
Men	3	1.15 (1.07 to 1.20)	54, 0.07
Women	5	1.22 (1.17 to 1.25)	60, 0.03
Never smokers			
All	8	1.17 (1.10 to 1.24)	72, 0.001
Men	4	1.13 (1.05 to 1.20)	0, 0.45
Women	5	1.16 (1.08 to 1.25)	80, 0.001
Healthy never smokers			
All	3	1.17 (1.09 to 1.25)	78, 0.01
Geographical region			
US	12	1.16 (1.11 to 1.20)	64, <0.001
Europe	12	1.23 (1.14 to 1.32)	92, <0.001
Asia	7	1.24 (1.07 to 1.42)	91, <0.001
Follow-up duration (years)			
<5	2	1.04 (0.95 to 1.10)	0, 0.73
5-10	11	1.20 (1.11 to 1.29)	87, <0.001
10-15	13	1.23 (1.15 to 1.31)	93, <0.001
15-20	3	1.22 (1.03 to 1.41)	81, 0.005
>20	2	1.34 (0.65 to 2.00)	87, 0.005
Anthropometric assessment			
Measured	29	1.20 (1.15 to 1.25)	90, <0.001
Self-reported	2	1.20 (1.16 to 1.24)	0, 0.35
Number of events			
<500	9	1.13 (1.03 to 1.23)	76, <0.001
500-1000	6	1.18 (1.07 to 1.30)	76, 0.001
1000-2000	3	1.16 (1.10 to 1.22)	0, 0.54
>2000	13	1.25 (1.18 to 1.31)	92, <0.001
Population body mass index			
<25	2	1.24 (1.09 to 1.39)	90, 0.002
≥25	2	1.13 (1.09 to 1.17)	0, 0.50
Study quality (stars)			
0–3	-	-	-
4–6	2	1.48 (1.04 to 1.92)	50, 0.16
7–9	29	1.20 (1.15 to 1.24)	91, <0.001
Adjustment for confounders			
Body mass index			
Yes	8	1.26 (1.17 to 1.35)	82, <0.001
No	23	1.18 (1.12 to 1.23)	89, <0.001
Physical activity			
Yes	19	1.22 (1.15 to 1.29)	93, <0.001
No	12	1.17 (1.10 to 1.23)	77, <0.001
Smoking status			
Yes	28	1.20 (1.15 to 1.25)	91, <0.001
No	3	1.22 (1.03 to 1.41)	74, 0.02
Alcohol consumption			
Yes	20	1.21 (1.16 to 1.26)	84, <0.001
No	11	1.19 (1.09 to 1.28)	93, <0.001
Body mass index, physical activity, smoking status, and alcohol drinking			
Yes	5	1.26 (1.18 to 1.35)	84, <0.001
No	26	1.18 (1.13 to 1.23)	88, <0.001
Adjustment for intermediates			
Blood pressure			
Yes	4	1.07 (0.99 to 1.15)	92, <0.001
No	27	1.23 (1.18 to 1.27)	82, <0.001
Serum cholesterol			
Yes	5	1.09 (1.01 to 1.17)	91, <0.001
No	26	1.22 (1.17 to 1.27)	82, <0.001
Type 2 diabetes			
Yes	6	1.11 (1.04 to 1.18)	93, <0.001
No	25	1.23 (1.18 to 1.28)	82, <0.001
Blood pressure, serum cholesterol, and type 2 diabetes			
Yes	4	1.07 (0.99 to 1.15)	92, <0.001
No	27	1.23 (1.18 to 1.27)	82, <0.001

doi: 10.1136/bmj.m3324 | *BMJ* 2020;370:m3324 | the bmj

Waist-to-thigh ratio

Two cohort studies comprising 2684 events among 22 866 participants reported risk estimates of all cause mortality in relation to waist-to-thigh ratio.[78 86] The hazard ratios associated with a 0.1 unit increment in waist-to-thigh ratio were 1.21 (95% confidence interval 1.03 to 1.39, I^2=97%; table 3), 1.19 (0.98 to 1.41, I^2=96%), and 1.15 (1.07 to 1.22, I^2=0%) in all participants, men, and women, respectively (fig S5 in appendix 1). We were unable to perform a non-linear dose-response analysis because only two studies were available for the analysis.

Body adiposity index

Four cohort studies involving 13 787 events of total mortality among 124 911 participants were included in the analysis of body adiposity index.[65 80 87 97] Summary hazard ratio for a 10% increment in body adiposity index was 1.17 (95% confidence interval 1.00 to 1.33), with high heterogeneity (I^2=75%, $P_{heterogeneity}$=0.007; fig 8, table 3). The results for men and women were 1.27 (1.04 to 1.50, I^2=48%, n=2) and 1.03 (1.00 to 1.05; I^2=91%, n=2), respectively. The non-linear dose-response analysis suggested a U shaped association between body adiposity index and all cause mortality risk ($P_{non\text{-}linearity}$<0.001, n=4; fig 9) with the lowest risk at a body adiposity index of 30% (hazard ratio 0.89, 0.84 to 0.95).

A body shape index

Nine cohort studies with 25 603 events among 716 596 participants were included in the analysis of A body shape index.[50 53 55 68 69 81 89 90 97] A 0.005 unit increment in A body shape index was associated with a 15% greater risk: hazard ratio 1.15 (95% confidence interval 1.10 to 1.20, I^2=87%, $P_{heterogeneity}$<0.001; fig 10, table 3). Summary hazard ratios were 1.22 (1.12 to 1.32, I^2=35%, n=3), 1.12 (1.09 to 1.15, I^2=0%, n=2), 1.17 (1.01 to 1.33; I^2=83%, n=5), and 1.11 (1.06 to 1.16, I^2=74%, n=5) in studies that controlled

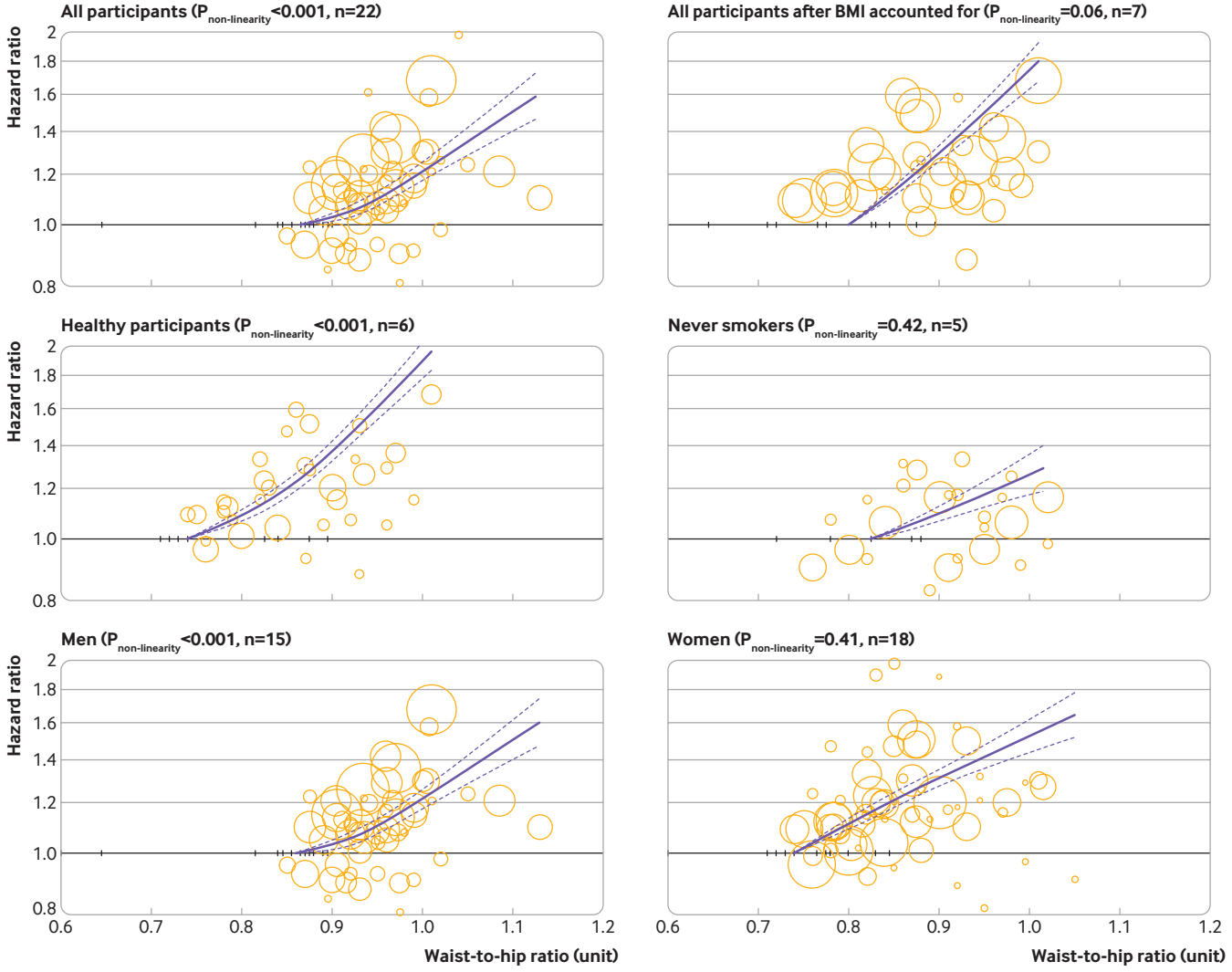
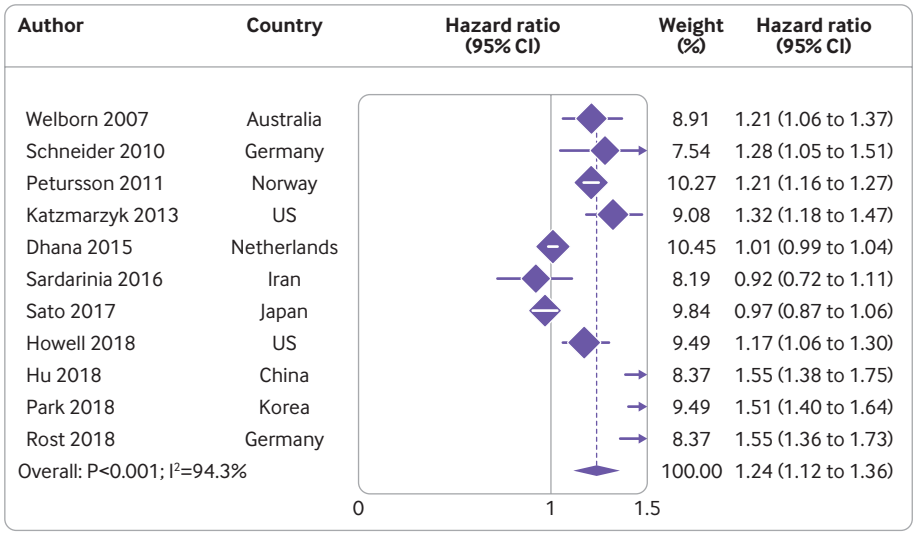


Fig 5 | Dose-response association of waist-to-hip ratio with risk of all cause mortality. Solid line represents non-linear dose response and dotted lines represent 95% confidence interval. Circles represent hazard ratio point estimates for adiposity categories from each study with circle size proportional to inverse of standard error. Small vertical black lines represent baseline adiposity category for each separate study



Note: Weights are from random effects analysis

Fig 6 | Summary hazard ratio of all cause mortality for 0.1 unit increment in waist-to-height ratio

for body mass index, healthy participants, men, and women, respectively. Geographical region, adjustment for body mass index, and exclusion of participants with pre-existing diseases were potential sources of heterogeneity.

Six studies reported data for the non-linear dose-response analysis.[55 68 69 81 90 97] A positive monotonic association was found between A body shape index and the risk of all cause mortality ($P_{non\text{-}linearity}$<0.001, fig 11).

Thigh circumference

Three cohort studies involving 25 412 participants and 4468 events were included in the analysis of thigh circumference.[56 78 102] We observed an 18% lower risk of total mortality associated with a 5 cm (1.97 inch) increase in thigh circumference in the analysis of all participants: hazard ratio 0.82 (95% confidence interval 0.75 to 0.89, I^2=54%, $P_{heterogeneity}$=0.11; table 3). The hazard ratios were 0.82 (0.73 to 0.90, I^2=0%, n=2) and 0.84 (0.63 to 1.06, I^2=80%, n=2) in men and women, respectively (fig S6 in appendix 1).

Hip circumference

Nine cohort studies with 25 618 cases among 297 598 participants were eligible for the analysis of hip circumference.[38 42 57 71 76 78 82 97 103] A 10 cm (3.94 inch) increment in hip circumference was associated with a 10% lower risk: hazard ratio 0.90 (95% confidence interval 0.81 to 0.99), with high heterogeneity (I^2=95%, $P_{heterogeneity}$<0.001; fig 12, table 3). The association was significant in women (0.90, 0.81 to 99, I^2=93%, n=7), but not in men (0.92, 0.73 to 1.10, I^2=94%, n=5). In an analysis stratified based on adjustment for body mass index and waist circumference, the association became stronger when body mass index and waist circumference were accounted for (0.78, 0.66 to 0.90, I^2=87%, n=4). In contrast, a significant positive association was found in studies without control for body mass index and waist circumference (1.04, 1.02 to 1.06, I^2=0%, n=5). Because the direction of the association depended completely on adjustment for body mass index and waist circumference, we did not perform subgroup analyses based on other variables.

Seven studies reported data for the non-linear dose-response analyses.[38 57 71 76 82 97 103] One study reported separate effect sizes with and without control for body mass index.[103] The risk of all cause mortality decreased linearly to hip circumference of 100 cm among studies that controlled for waist circumference and body mass index (hazard $ratio_{100cm}$ 0.70, 95% confidence interval 0.64 to 0.77) and then reached a plateau ($P_{non\text{-}linearity}$<0.001, n=4; fig 13, upper panel). In contrast, a U shaped association was observed in the analysis of

Table 3 | Summary hazard ratios of all cause mortality in relation to central obesity measures

Anthropometric measures	Comparison (increase)	No of studies	No of participants	No of events	Summary hazard ratio (95% CI)	Heterogeneity, I^2 (%)
Waist circumference	10 cm (3.94 inches)	50	2 056 428	128 842	1.11 (1.08 to 1.13)	88
Waist-to-hip ratio	0.1 unit	31	1 112 816	75 183	1.20 (1.15 to 1.25)	90
Waist-to-height ratio	0.1 unit	11	760 190	23 959	1.24 (1.12 to 1.36)	94
Waist-to-thigh ratio	0.1 unit	2	22 866	2684	1.21 (1.03 to 1.39)	97
Body adiposity index	10%	4	124 911	13 787	1.17 (1.00 to 1.33)	75
A body shape index	0.005 unit	9	716 596	25 603	1.15 (1.10 to 1.20)	87
Thigh circumference	5 cm (1.97 inches)	3	25 412	4468	0.82 (0.75 to 0.89)	54
Hip circumference	10 cm (3.94 inches)	9	297 598	25 618	0.90 (081 to 0.99)	95

doi: 10.1136/bmj.m3324 | *BMJ* 2020;370:m3324 | the bmj

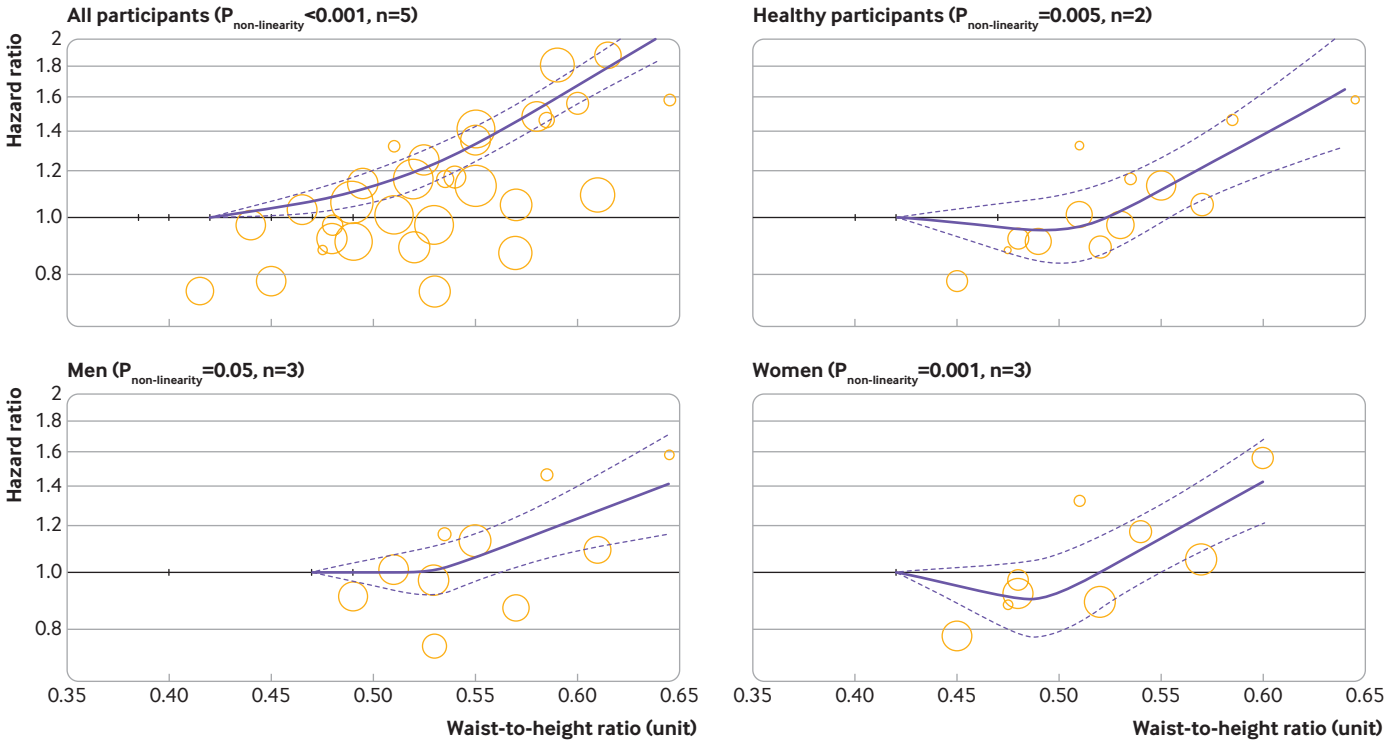
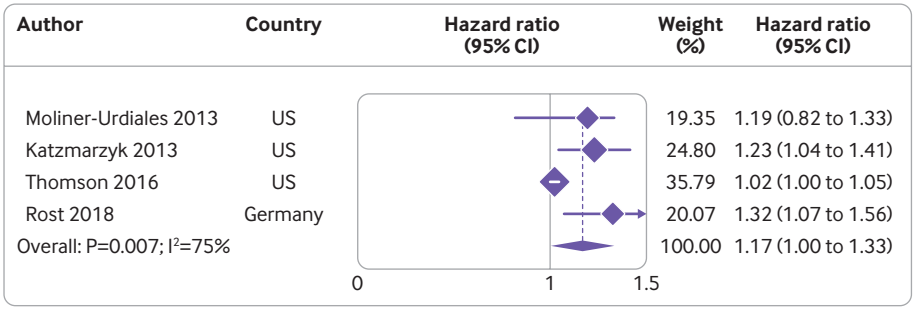


Fig 7 | Dose-response association of waist-to-height ratio with risk of all-cause mortality. Solid line represents non-linear dose response and dotted lines represent 95% confidence interval. Circles represent hazard ratio point estimates for adiposity categories from each study with circle size proportional to inverse of standard error. Small vertical black lines represent baseline adiposity category for each separate study

four studies that did not control for body mass index and waist circumference ($P_{non\text{-}linearity}$<0.001, n=4; fig 13, lower panel), with lowest risk at 103 cm (hazard ratio$_{103cm}$ 0.86, 0.83 to 0.89).

Comparison of associations across different measures of central fatness

To compare the associations of indices of central fatness with all cause mortality risk, we calculated hazard ratio in each study for a one standard deviation increment in anthropometric measures and pooled the results with the use of a random effects model. However, in that analysis, the number of studies might differ with the number of studies included in the main analyses because we were unable to calculate standard deviation values in some studies. Some studies reported hazard ratios for one standard deviation, but the exact amount of standard deviation was not reported in the text. Two studies (one publication) reported effect size for a one standard deviation increment in waist-to-hip ratio, waist-to-height ratio, and hip circumference, but the exact standard deviations were not reported in the text, and so were included only in the analyses of standard deviation.[36] Another two cohort studies reported effect size for a one standard deviation increment in waist-to-height ratio, and again, did not report exact standard deviation values[60 69]; therefore, these studies were included only in the standard deviation analysis. Table 4 and figs S7-S14 (appendix 1) present summary hazard ratios for one standard deviation increments in anthropometric measures.



Note: Weights are from random effects analysis

Fig 8 | Summary hazard ratio of all cause mortality for 10% increment in body adiposity index

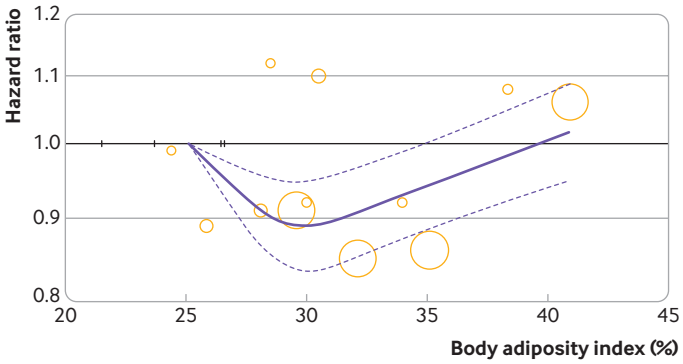


Fig 9 | Dose-response association of body adiposity index with the risk of all cause mortality ($P_{non\text{-}linearity}$<0.001, n=4). Solid line represents the non-linear dose response and dotted lines represent 95% confidence interval. Circles represent the hazard ratio point estimates for adiposity categories from each study with circle size proportional to inverse of standard error. Small vertical black lines represent baseline adiposity category for each separate study

Discussion

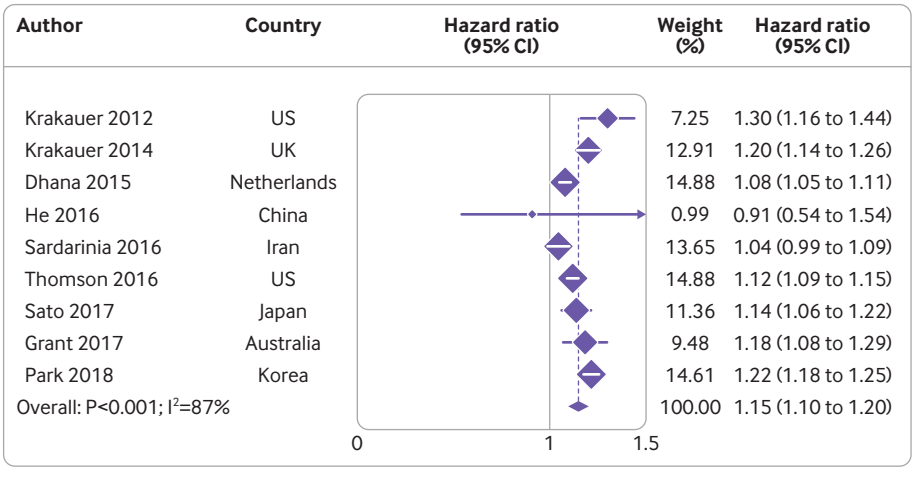
Principal findings

In this systematic review and dose-response meta-analysis, we pooled data from 72 prospective cohort studies to present a relatively comprehensive overview of the association of indices of central fatness with all cause mortality risk. We found that most indices of abdominal adiposity including waist circumference, waist-to-hip ratio, waist-to-height ratio, waist-to-thigh ratio, and A body shape index were significantly and positively associated with a higher all cause mortality risk. We found that the associations remained significant after body mass index was accounted for, which indicated that abdominal deposition of fat, independent of overall obesity, is associated with a higher risk. We performed sex specific non-linear dose-response analyses that showed the risk of total mortality did not materially change within the initial units of central fatness; this was followed by a sharp and significant increase in the risk. However, this study showed that two indices of central fatness—thigh circumference and hip circumference—were inversely associated with all cause mortality risk.

Mechanisms

We know that adiposity is associated with a higher risk of premature death. Adiposity exerts adverse impacts on systemic inflammation,[105] oxidative stress,[106] insulin resistance,[107] blood pressure,[108] lipid profile,[109] and endothelial dysfunction[110] and is linked to a greater risk of cardiovascular disease,[111] site specific cancers,[112] kidney disease,[113] and neurological disorders.[114] The number of people with overweight and obesity has doubled during the past 40 years. As a result, approximately one third of the world's populations are overweight or obese.[115]

Body mass index, a measure of overall adiposity, is easy to obtain and has clear categories. Therefore, body mass index is the most frequent anthropometric measure used to define and classify adiposity. However, because of the relative inability of body mass index to distinguish between lean mass and fat mass, and to differentiate between overall adiposity and abdominal adiposity, indices of central fatness might be more reliable indicators of adiposity. Body mass index might be increased because of muscle development rather than fat accumulation from overeating.[116] Higher muscle mass could reduce the risk of premature death.[117] However, although higher body mass index is associated with a higher risk of morbidity and mortality, substantial heterogeneity was found among people with similar body mass index values. Studies have shown that among people who were categorised into equal body mass index categories, those with abdominal adiposity (reflected by large waist circumference) had an increased risk of coronary heart disease and type 2 diabetes.[118 119] Abdominal adiposity, reflected mainly by large waist circumference, is highly correlated with detrimental visceral fat[120 121] and is a reflection of visceral fat deposition.[122] Having a larger waist circumference, even within the normal weight range, is associated



Note: Weights are from random effects analysis

Fig 10 | Summary hazard ratio of all cause mortality for 0.005 unit increment in A body shape index

doi: 10.1136/bmj.m3324 | *BMJ* 2020;370:m3324 | the bmj

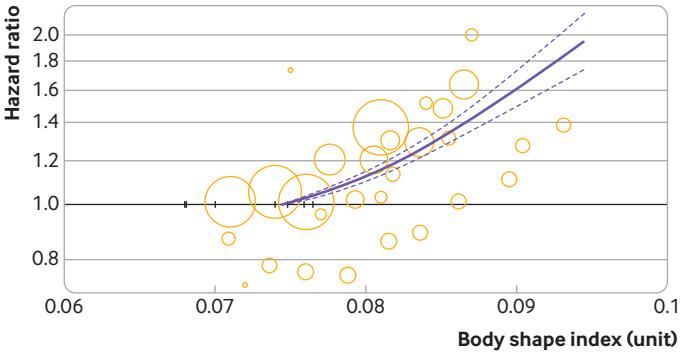


Fig 11 | Dose-response association of A body shape index with risk of all cause mortality ($P_{non\text{-}linearity}$<0.001, n=6). Solid line represents non-linear dose response and dotted lines represent 95% confidence interval. Circles represent the hazard ratio point estimates for adiposity categories from each study with circle size proportional to inverse of standard error. Small vertical black lines represent baseline adiposity category for each separate study

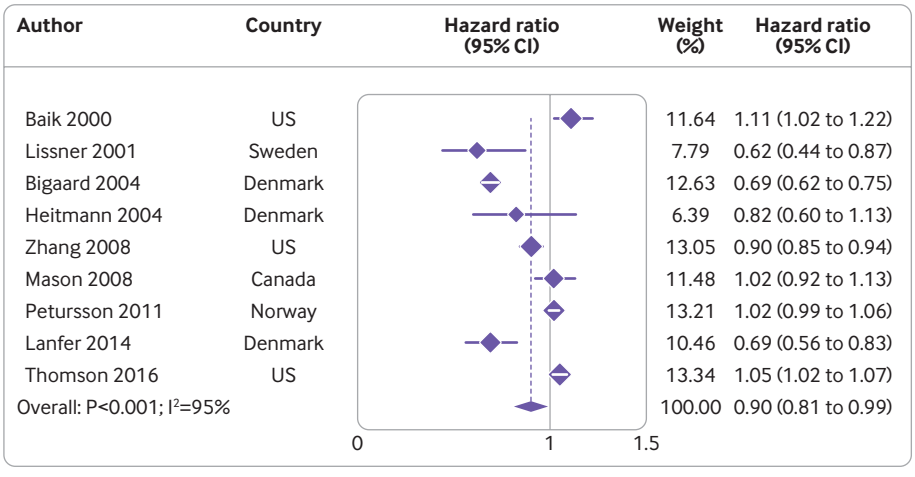
with cardiometabolic abnormalities[123] and higher risk of mortality and morbidity.[61 124 125]

Although waist circumference shows the regional fat distribution, it is strongly correlated with body mass index.[126] The waist-to-hip ratio might provide better information on regional fat distribution because it considers detrimental visceral fat and beneficial gluteal fat and muscle.[6] The waist-to-hip ratio is less strongly correlated with body mass index than waist circumference and has less potential for collinearity; therefore, it could be a more specific surrogate for regional body fat distribution. Larger waist circumference indicates higher detrimental visceral fat mass, while greater waist-to-hip ratio indicates higher detrimental visceral fat mass and lower beneficial gluteofemoral fat and muscle mass. The non-linear dose-response analyses indicated that the slope of the curvilinear associations was steeper in the analyses of waist-to-hip ratio compared with waist circumference, especially in the subgroup of studies that controlled for body mass index. However, height is easier to measure than hip circumference, and so waist-to-height ratio could be used as an appropriate alternative to waist-to-hip ratio because it controls for body size by using height. Waist-to-height ratio could have greater correlation with cardiometabolic risk factors than body mass index.[5]

Considering the limitations of the current measures of general and abdominal adiposity, including body mass index (inability to distinguish lean mass from fat mass), waist circumference (strong correlation with body mass index), and waist-to-hip ratio (difficulty in measuring hip circumference), a new anthropometric measure entitled A body shape index has been developed.[68] This measure is calculated by dividing waist circumference by (body mass index$^{2/3}$×height$^{1/2}$). The A body shape index has a slight correlation with body mass index, height, and weight, and so could be independent of other anthropometric variables in predicting mortality.[127] In the present review, we found a positive monotonic association between A body shape index and the risk of all cause mortality; the risk of premature death increased proportionally with increasing A body shape index values. The results are similar to those of the National Health and Nutrition Examination Survey, which indicated a positive linear association between A body shape index and risk of premature death.[68]

Comparison with other studies

For each 10 cm increase in waist circumference, we found an 8% and a 12% higher risk of all cause mortality in men and women, respectively. The results were relatively weaker than those of a recent pooled analysis of 11 prospective cohort studies in Western countries, which suggested a 7% and a 9% higher risk for a 5 cm increase in waist circumference in men and women, respectively (equivalent to a 14% and an 18% higher risk for a 10 cm increase, respectively).[15] The weaker associations found in our study might be owing to the inclusion of large scale Western prospective cohort studies only in the previous pooled analysis.



Note: Weights are from random effects analysis

Fig 12 | Summary hazard ratio of all cause mortality for 10 cm increment in hip circumference

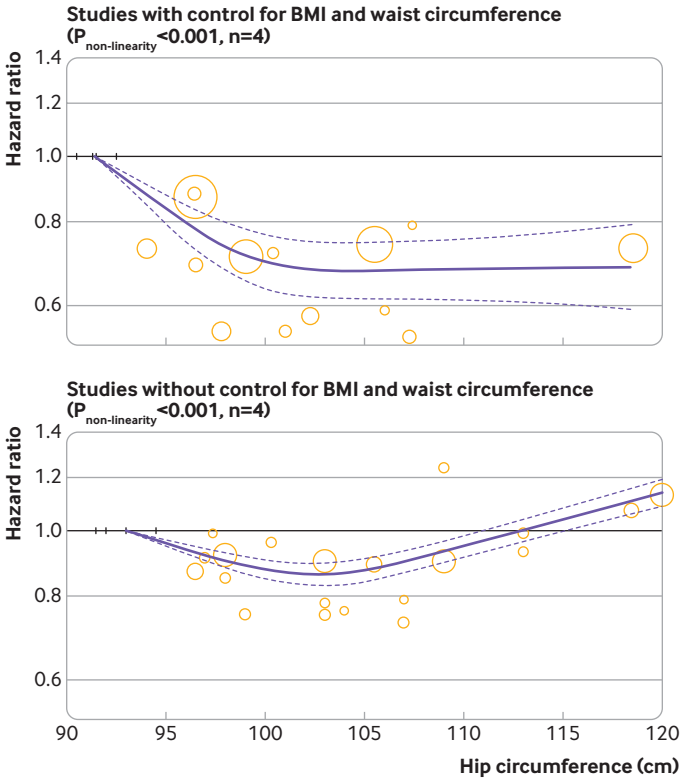


Fig 13 | Dose-response association of hip circumference with risk of all cause mortality. Solid line represents non-linear dose response and dotted lines represent 95% confidence interval. Circles represent hazard ratio point estimates for adiposity categories from each study with circle size proportional to inverse of standard error. Small vertical black lines represent baseline adiposity category for each separate study

We included 15 non-Western cohort studies, which reported weaker associations.

We also found a relatively J shaped association between waist circumference and all cause mortality risk in the analyses of men. The lowest risk was observed for a waist circumference of 90 cm in the analyses of all participants, healthy participants, and especially in studies with more than 10 years of follow-up. When we limited the analysis of men to studies that controlled for body mass index, the risk did not change up to a waist circumference of 100 cm, and then increased sharply and linearly. Only four studies were available for the analysis of men who were never smokers, and the results showed no significant association. For women, we found a cut-off point of 80 cm in all women, healthy women, women who were never smokers, and healthy women who were never smokers.

Previous studies analysing the shape of the association between waist circumference and total mortality risk have inconsistent results. Some large scale prospective cohort studies showed a J shaped relation,[43 51 52 61 67 83] while others suggested a positive linear association.[103] A pooled analysis of 650 000 adults in Western countries found a J shaped association for men and a positive linear association for women.[15] The present study found cut-off points of 80 for women and 90 for men, after which the risk of mortality showed a sharp and linear increment in the risk. However, owing to the inclusion of smokers and participants with pre-existing disease, the results for all participants must be interpreted cautiously. Additionally, the analysis of aggregate data will lead to underestimation of relations, and we had to use several approximations that will have affected the analyses. Therefore, the shape of the curves obtained in this review must be interpreted with caution.

Current guidelines recommend different criteria to define people with abdominal adiposity and high cardiometabolic risk. The executive summary of the third report of the National Cholesterol Education Programme expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) recommends cut-off points of waist circumference greater than 102 cm for men and greater than 88 cm for women to define abdominal adiposity in the US.[128] According to the definition of the International Diabetes Federation, central adiposity is defined as a waist circumference of at least 94 cm in European countries and at least 90 cm in Asian and African countries for men, and at least 80 cm in European, Asian, and African countries for women.[129] The European Group for the Study of Insulin Resistance considerers a waist circumference larger than 94 and 80 cm defines abdominal adiposity in men and women, respectively.[130] However, unlike the other three definitions, the World Health Organization defined central adiposity as a waist-to-hip ratio greater than 0.90 in men and greater than 0.85 in women.[131]

For waist-to-height ratio, the existing literature suggests a cut-off point of 0.50 for determining abdominal adiposity and cardiometabolic risk.[5 132-135] In support of current evidence, we found a cut-off point of 0.50 for men and women, after which the risk of all cause mortality increased sharply and linearly; the risk increased significantly at a waist-to-height ratio of 0.55. In the analyses of waist-to-hip ratio, a positive monotonic association was found in men and women, in which the risk increased from baseline up to a waist-to-hip ratio of 1.1.

In the analyses of waist circumference, waist-to-hip ratio, waist-to-height ratio, and A body shape index, the results were much stronger in the subgroups of studies that controlled for body mass index in their multivariable analyses than in subgroups that did not control for body mass index. Of the 72 prospective cohort studies in the present review, 13 reported hazard ratios with and without adjustment for body mass index; of these, 11 studies (10 publications) reported stronger effect sizes in the models that controlled for body mass index.[35 39 41 54 60-62 81 83 103] Only two cohort studies reported weaker effect sizes in the models without adjustment for body mass index.[43 67] Adjustment for body mass index could decrease potential confounding by pre-existing disease and pathological conditions, which in turn are associated with lower lean body mass.[136] Another explanation is that body mass index reflects both fat and lean mass, while waist circumference and other indices of central

doi: 10.1136/bmj.m3324 | *BMJ* 2020;370:m3324 | the bmj

Table 4 | Summary hazard ratios of all cause mortality for one standard deviation increment in central obesity measures

Anthropometric measures	SD values	No of studies	No of participants	No of events	Summary hazard ratio (95% CI)	Heterogeneity, I^2 (%)
Thigh circumference	5.2 cm (2.05 inches)	3	25 412	4468	0.82 (0.76 to 0.89)	47
Hip circumference	8 cm (3.15 inches)	11	303 296	26 959	0.93 (0.87 to 0.99)	92
Body adiposity index	8%	4	124 911	13 787	1.10 (1.01 to 1.19)	73
Waist circumference	9.8 cm (3.86 inches)	51	2 132 756	136 825	1.12 (1.09 to 1.14)	85
Waist-to-hip ratio	0.07 unit	33	1 112 816	75 183	1.14 (1.11 to 1.18)	93
Waist-to-height ratio	0.06 unit	14	785 125	24 870	1.17 (1.10 to 1.24)	91
A body shape index	0.006 unit	9	716 596	25 603	1.17 (1.13 to 1.21)	73
Waist-to-thigh ratio	0.14 unit	2	22 866	2684	1.32 (1.01 to 1.62)	89

SD=standard deviation.

adiposity mainly reflect fat mass. After adjusting for body mass index, waist circumference mainly reflects total and deleterious visceral fat, and as a result, shows stronger association with mortality risk. Therefore, by combining central adiposity measures with body mass index, a more accurate estimation could be made of the association of adiposity with mortality risk.

In the non-linear dose-response meta-analyses of waist circumference and waist-to-hip ratio, the slope of the curvilinear association increased sharply after adjustment for body mass index. A large prospective cohort study in Europe suggested a J shaped association between waist circumference and risk of death before adjustment for body mass index. Additionally, a strong positive linear association was observed after adjustment for body mass index, suggesting that both measures of general and abdominal adiposity should be considered when determining the risk of premature death.[83] Although in the present review 13 prospective cohort studies reported the hazard ratios with and without adjustment for body mass index, different primary studies were still included in the subgroups with and without controlling for body mass index. Therefore, the observed differences in the analyses with and without controlling for body mass index could be subject to confounding.

We also found a significant inverse association between larger hip circumference and thigh circumference and the risk of mortality. Deposition of fat in gluteofemoral region, irrespective of gender, is thought to be independently associated with better lipid and glucose profiles, and might have protective effects against cardiovascular and metabolic risk.[6] However, we found that the direction of the association between hip circumference and mortality was different among studies with and without controlling for waist circumference and body mass index. An inverse association was found among studies that controlled for waist circumference and body mass index, and in contrast, a U shaped association was observed among studies that did not control for waist circumference and body mass index.

Hip circumference measures gluteal subcutaneous adipose tissue and muscle mass.[6] In contrast, waist circumference is a reflection of subcutaneous and visceral adipose tissue. However, hip circumference is highly correlated with body mass index and a correlation exists between body mass index and waist circumference.[12] Therefore, larger hip circumference might reflect higher body mass index and waist circumference, which could partly explain the U shaped association found in studies that did not control for waist circumference.[38] Adjusting hip circumference, which reflects beneficial gluteal fat, for waist circumference, which incorporates deleterious visceral fat, might allow a more precise estimation of the beneficial effects of gluteofemoral fat.[137] However, different prospective cohort studies were included in the subgroups with and without controlling for waist circumference and body mass index. Only one prospective cohort study reported the hazard ratios of all cause mortality for hip circumference with and without controlling for waist circumference and body mass index.[103] These results are from different studies and therefore could be subject to confounding.

Two recent comprehensive meta-analyses of more than 200 prospective cohort studies were performed to evaluate the association between overall adiposity, reflected by body mass index, and the risk of all cause mortality.[12] Both low and high body mass index were found to be associated with a significantly higher risk. The results indicated a U shaped and a J shaped association between body mass index and the risk of all cause mortality in the general population and healthy never smokers, respectively. However, we found inconsistent results. Our findings indicated a modest increase in the risk of all cause mortality in participants with small waist circumference in men, and in women who were never smokers and healthy women who were never smokers. The higher risk of mortality in underweight participants by body mass index has been attributed to reverse causation and potential confounding by smoking, recent weight loss, and pre-existing disease, which might result in a low body mass index.[138 139]

The body mass index incorporates both lean mass and fat mass, and so being underweight by body mass index reflects lower beneficial lean mass and detrimental visceral fat mass. In contrast, abdominal adiposity is a measure of subcutaneous and visceral fat mass, therefore smaller waist circumference might reflect lower detrimental visceral fat mass and does not necessarily reflect lower lean body mass. This information could partly explain the observed difference in the risk of mortality in participants with low body mass index and small waist circumference.

Another explanation is that although a strong correlation exists between body mass index and waist circumference, small waist circumference does not necessarily reflect low body mass index. Participants could be normal weight, overweight, or obese by body mass index, and at the same time, have either small or large waist circumference. A prospective evaluation among 150 000 women who were postmenopausal in the US indicated that participants could be normal weight, overweight, or even obese by body mass index, but could have small waist circumference.[140] Therefore, smaller waist circumference does not necessarily reflect lower body mass index and so is not necessarily associated with a higher mortality risk.

We also performed an additional analysis to compare the associations across different measures of central fatness. The results showed that waist-to-thigh ratio and A body shape index have the strongest associations with mortality risk among anthropometric measures studied in this review. However, some important differences exist, such as the number of primary studies included in the analysis of each anthropometric measure (eg, 51 studies for waist circumference and two studies for waist-to-thigh ratio), and confounding variables were accounted for in each analysis. Additionally, these results reflect the associations in the general populations. Smoking status and pre-existing disease might confound the association of indices of central obesity with all cause mortality risk. Therefore, our findings relating to the stronger association of waist-to-thigh ratio and A body shape index with all cause mortality risk should be interpreted cautiously.

Strengths and limitations of this study

Some important limitations must be noted when interpreting the results. Although we excluded studies specifically conducted among patients with diseases, some original studies still included patients with existing diseases and potentially undiagnosed diseases at baseline. Therefore, potential confounding by pre-existing diseases must be considered. Furthermore, in the analyses of waist circumference and waist-to-hip ratio, only eight studies reported sufficient data for never smokers. Additionally, we were unable to perform such analyses for waist-to-height ratio, waist-to-thigh ratio, thigh circumference, hip circumference, body adiposity index, and A body shape index. Therefore, the results might have been affected by confounding effects of smoking. However, for waist circumference and waist-to-hip ratio, the results for never smokers were approximately similar to those of the main analyses. We performed sex specific non-linear dose-response analyses of never smokers and healthy participants only in the analysis of waist circumference, and we were unable to perform such analyses for other anthropometric measures.

Only 14 studies for waist circumference, nine studies for waist-to-hip ratio, four studies for waist-to-height ratio, and two studies for A body shape index reported data for healthy participants; no study was found to test the associations for waist-to-thigh ratio, hip circumference, thigh circumference, and body adiposity index in healthy participants. Additionally, most of these studies excluded only participants with a history of cancer and cardiovascular disease at baseline. Therefore, residual confounding from undiagnosed pre-existing disease such as respiratory disease and kidney failure must be noted. Furthermore, only two, three, and four studies were available for the analyses of waist-to-thigh ratio, thigh circumference, and body adiposity index, respectively. Additionally, the non-linear dose-response analyses of waist-to-height ratio, body adiposity index, and A body shape index are based on relatively few studies. Therefore, further studies should assess the degree and the shape of the associations for these measures. Almost all studies included in the present review assessed baseline anthropometric measures and potential changes during the follow-up period were not considered in their analyses. Furthermore, existing evidence suggests that the strength of the association between adiposity and the risk of mortality decreases with increasing age.[141 142] Our results also indicated that the association became non-significant (for waist circumference) or weakened substantially (for waist-to-hip ratio) in participants aged 60 years and older. However, we were unable to test the associations in different subgroups of age for different measures of central fatness, and so future research should test the degree and the shape of the association for different measures of central fatness.

Although indices of central fatness can reflect body fat distribution, they have low capability to measure total body fat,[136] and so they can be used as supplementary approaches, in parallel with body mass index, to determine cardiometabolic risk. Finally, analysis of aggregate data would have led to underestimation of relations, and we had to use several approximations that would have affected the analyses. Therefore, some subtle issues such as identification of thresholds and the exact shape of the curves cannot be reliably observed in such data.

The present study also has several strengths. We gathered all the evidence relating to the association of all measures of central fatness with all cause mortality risk. We included 72 high quality prospective cohort studies with more than 2.53 million participants, which enabled us to test the associations in different subgroups. We performed several subgroup analyses based on study duration, geographical location, number of events, and adjustment for main confounders. We performed sex specific non-linear dose-response analyses for almost all exposures, especially for waist circumference, in which we performed sex specific non-linear analyses in never smokers and healthy participants. We found sex specific cut-off points in the analyses of waist circumference, waist-to-hip ratio, and waist-to-height ratio that confirmed current recommendations for classification of adults to identify those with abdominal adiposity and cardiometabolic risk. Finally, we compared the associations across

different measures of central fatness that showed waist-to-thigh ratio and A body shape index had the strongest associations with all cause mortality risk. However, limited studies were found for waist-to-thigh ratio and A body shape index, therefore we cannot speculate that these indices are the best anthropometric measures to predict premature death.

Conclusions

The present meta-analysis of 72 prospective cohort studies indicated that most indices of central fatness including waist circumference, waist-to-hip ratio, waist-to-height ratio, body adiposity index, and A body shape index, independent of overall adiposity, were positively and significantly associated with a higher all cause mortality risk. Larger hip circumference and thigh circumference were associated with a lower risk. Our results suggest that measures of central adiposity could be used as a supplementary approach, in combination with body mass index, to determine the risk of premature death. However, analysis of aggregate data would have led to underestimation of relations, and several methodological approximations would have affected the analyses. Therefore, an individual participant data meta-analysis of studies with multiple markers (including body mass index) is needed to assess the shape of these relations and their comparison or incremental value with body mass index. Additionally, more accurate estimations of the associations are needed, especially in healthy never smokers.

AUTHOR AFFILIATIONS

[1]Food Safety Research Center (salt), Semnan University of Medical Sciences, Semnan, Iran

[2]Department of Community Nutrition, School of Nutritional Science and Dietetics, Tehran University of Medical Sciences, PO Box 14155/6117, Tehran, Iran

[3]Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[4]Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[5]Nursing Care Research Center, Semnan University of Medical Sciences, Semnan, Iran

[6]Clinical Nutrition and Risk Factor Modification Centre, St Michael's Hospital, Toronto, Ontario, Canada

[7]Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

[8]Toronto 3D Knowledge Synthesis & Clinical Trials Unit, St Michael's Hospital, Toronto, Ontario, Canada

Contributors: AJ contributed to the study conception, literature search, data extraction, data analysis, and manuscript drafting. MSZ contributed to the literature search, data extraction, and manuscript drafting. SS contributed to manuscript drafting and approving the final manuscript. TAK contributed to the data analysis and approving the final manuscript. SS-B contributed to the study conception, data analysis, and manuscript drafting. All authors acknowledge full responsibility for the analyses and interpretation of the report. All authors have read and approved the final manuscript. SS-B is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: No separate funding was necessary for undertaking this systematic review.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work; TAK reports grants from Canadian Institutes of Health Research, grants from International Life Sciences Institute, grants from National Honey Board, personal fees from Calorie Control Council, outside the submitted work.

Ethical approval: Not required.

Data sharing: No additional data available.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We plan to disseminate these findings to participants in our annual newsletter.

Provenance and peer review statement: Not commissioned; externally peer reviewed.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

1 Aune D, Sen A, Prasad M, et al. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ* 2016;353:i2156. doi:10.1136/bmj.i2156

2 Di Angelantonio E, Bhupathiraju ShN, Wormser D, et al, Global BMI Mortality Collaboration. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;388:776-86. doi:10.1016/S0140-6736(16)30175-1

3 Kok P, Seidell JC, Meinders AE. [The value and limitations of the body mass index (BMI) in the assessment of the health risks of overweight and obesity]. *Ned Tijdschr Geneeskd* 2004;148:2379-82.

4 Després J-P. Body fat distribution and risk of cardiovascular disease: an update. *Circulation* 2012;126:1301-13. doi:10.1161/CIRCULATIONAHA.111.067264

5 Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev* 2012;13:275-86. doi:10.1111/j.1467-789X.2011.00952.x

6 Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. *Int J Obes (Lond)* 2010;34:949-59. doi:10.1038/ijo.2009.286

7 Cornier MA, Després JP, Davis N, et al, American Heart Association Obesity Committee of the Council on Nutrition, Physical Activity and Metabolism, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Stroke Council. Assessing adiposity: a scientific statement from the American Heart Association. *Circulation* 2011;124:1996-2019. doi:10.1161/CIR.0b013e318233bc6a

8 Nyamdorj R, Qiao Q, Lam TH, et al, Decoda Study Group. BMI compared with central obesity indicators in relation to diabetes and hypertension in Asians. *Obesity (Silver Spring)* 2008;16:1622-35. doi:10.1038/oby.2008.73

9 Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *Am J Clin Nutr* 2005;81:555-63. doi:10.1093/ajcn/81.3.555

10 Yusuf S, Hawken S, Ounpuu S, et al, INTERHEART Study Investigators. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* 2005;366:1640-9. doi:10.1016/S0140-6736(05)67663-5

11 Connor Gorber S, Tremblay M, Moher D, Gorber B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes Rev* 2007;8:307-26. doi:10.1111/j.1467-789X.2007.00347.x

12 Carmienke S, Freitag MH, Pischon T, et al. General and abdominal obesity parameters and their combination in relation to mortality: a systematic review and meta-regression analysis. *Eur J Clin Nutr* 2013;67:573-85. doi:10.1038/ejcn.2013.61

13 de Hollander EL, Bemelmans WJ, Boshuizen HC, et al, WC elderly collaborators. The association between waist circumference and risk

of mortality considering body mass index in 65- to 74-year-olds: a meta-analysis of 29 cohorts involving more than 58 000 elderly persons. *Int J Epidemiol* 2012;41:805-17. doi:10.1093/ije/dys008
14 Ji M, Zhang S, An R. Effectiveness of A Body Shape Index (ABSI) in predicting chronic diseases and mortality: a systematic review and meta-analysis. *Obes Rev* 2018;19:737-59. doi:10.1111/obr.12666
15 A pooled analysis of waist circumference and mortality in 650 000 adults. Mayo Clinic Proceedings; 2014. Elsevier.
16 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264-9, W64. doi:10.7326/0003-4819-151-4-200908180-00135
17 Beller EM, Glasziou PP, Altman DG, et al, PRISMA for Abstracts Group. PRISMA for Abstracts: reporting systematic reviews in journal and conference abstracts. *PLoS Med* 2013;10:e1001419. doi:10.1371/journal.pmed.1001419
18 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603-5. doi:10.1007/s10654-010-9491-z
19 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88. doi:10.1016/0197-2456(86)90046-2
20 Symons MJ, Moore DT. Hazard rate ratio and prospective epidemiological studies. *J Clin Epidemiol* 2002;55:893-9. doi:10.1016/S0895-4356(02)00443-2
21 Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. *Epidemiology* 1993;4:218-28. doi:10.1097/00001648-199305000-00005
22 Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose–response data. *Stata J* 2006;6:40-57. doi:10.1177/1536867X0600600103
23 Jayedi A, Rashidy-Pour A, Parohan M, Zargar MS, Shab-Bidar S. Dietary antioxidants, circulating antioxidant concentrations, total antioxidant capacity, and risk of all-cause mortality: a systematic review and dose-response meta-analysis of prospective observational studies. *Adv Nutr* 2018;9:701-16. doi:10.1093/advances/nmy040
24 Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr* 2017;105:1462-73. doi:10.3945/ajcn.117.153148
25 Jelicic Kadic A, Vucic K, Dosenovic S, Sapunar D, Puljak L. Extracting data from figures with software was faster, with higher interrater reliability than manual extraction. *J Clin Epidemiol* 2016;74:119-23. doi:10.1016/j.jclinepi.2016.01.002
26 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60. doi:10.1136/bmj.327.7414.557
27 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34. doi:10.1136/bmj.315.7109.629
28 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101. doi:10.2307/2533446
29 Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions*. John Wiley & Sons, 2011.
30 Harrell FEJ. *Regression Modeling Strategies-with Applications to Linear Models, Logistic Regression, and Survival Analysis: Springer Series in Statistics*. Springer, 2001. doi:10.1007/978-1-4757-3462-1
31 Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response meta-analysis for aggregated data. *Stat Methods Med Res* 2019;28:1579-96. doi:10.1177/0962280218773122
32 Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992;135:1301-9. doi:10.1093/oxfordjournals.aje.a116237
33 Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol* 2012;175:66-73. doi:10.1093/aje/kwr265
34 Hamling J, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med* 2008;27:954-70. doi:10.1002/sim.3013
35 Warren Andersen S, Shu X-O, Gao Y-T, et al. Prospective cohort study of central adiposity and risk of death in middle aged and elderly chinese. *PLoS One* 2015;10:e0138429. doi:10.1371/journal.pone.0138429
36 Taylor AE, Ebrahim S, Ben-Shlomo Y, et al. Comparison of the associations of body mass index and measures of central adiposity and fat mass with coronary heart disease, diabetes, and all-cause mortality: a study using data from 4 UK cohorts. *Am J Clin Nutr* 2010;91:547-56. doi:10.3945/ajcn.2009.28757
37 Adegbija O, Hoy WE, Dong B, Wang Z. Body mass index and waist circumference as predictors of all-cause mortality in an Aboriginal Australian community. *Obes Res Clin Pract* 2017;11:19-26. doi:10.1016/j.orcp.2016.06.003
38 Baik I, Ascherio A, Rimm EB, et al. Adiposity and mortality in men. *Am J Epidemiol* 2000;152:264-71. doi:10.1093/aje/152.3.264
39 Beleigoli AM, Boersma E, Diniz MdeF, Lima-Costa MF, Ribeiro AL. Overweight and class I obesity are associated with lower 10-year risk of mortality in Brazilian older adults: the Bambuí Cohort Study of Ageing. *PLoS One* 2012;7:e52111. doi:10.1371/journal.pone.0052111
40 Bellocco R, Jia C, Ye W, Lagerros YT. Effects of physical activity, body mass index, waist-to-hip ratio and waist circumference on total mortality risk in the Swedish National March Cohort. *Eur J Epidemiol* 2010;25:777-88. doi:10.1007/s10654-010-9497-6
41 Berentzen TL, Jakobsen MU, Halkjaer J, Tjønneland A, Overvad K, Sørensen TI. Changes in waist circumference and mortality in middle-aged men and women. *PLoS One* 2010;5:e13097. doi:10.1371/journal.pone.0013097
42 Bigaard J, Frederiksen K, Tjønneland A, et al. Waist and hip circumferences and all-cause mortality: usefulness of the waist-to-hip ratio?*Int J Obes Relat Metab Disord* 2004;28:741-7. doi:10.1038/sj.ijo.0802635
43 Boggs DA, Rosenberg L, Cozier YC, et al. General and abdominal obesity and risk of death among black women. *N Engl J Med* 2011;365:901-8. doi:10.1056/NEJMoa1104119
44 Bombelli M, Facchetti R, Fodri D, et al. Impact of body mass index and waist circumference on the cardiovascular risk and all-cause death in a general population: data from the PAMELA study. *Nutr Metab Cardiovasc Dis* 2013;23:650-6. doi:10.1016/j.numecd.2012.01.004
45 Bowman K, Atkins JL, Delgado J, et al. Central adiposity and the overweight risk paradox in aging: follow-up of 130,473 UK Biobank participants. *Am J Clin Nutr* 2017;106:130-5. doi:10.3945/ajcn.116.147157
46 Calori G, Lattuada G, Ragogna F, et al. Fatty liver index and mortality: the Cremona study in the 15th year of follow-up. *Hepatology* 2011;54:145-52. doi:10.1002/hep.24356
47 Cameron AJ, Dunstan DW, Owen N, et al. Health and mortality consequences of abdominal obesity: evidence from the AusDiab study. *Med J Aust* 2009;191:202-8. doi:10.5694/j.1326-5377.2009.tb02753.x
48 Cohen SS, Signorello LB, Cope EL, et al. Obesity and all-cause mortality among black adults and white adults. *Am J Epidemiol* 2012;176:431-42. doi:10.1093/aje/kws032
49 Danon-Hersch N, Fustinoni S, Bovet P, Spagnoli J, Santos-Eggimann B. Association between adiposity and disability in the Lc65+ cohort. *J Nutr Health Aging* 2017;21:799-810. doi:10.1007/s12603-016-0813-z
50 Dhana K, Kavousi M, Ikram MA, Tiemeier HW, Hofman A, Franco OH. Body shape index in comparison with other anthropometric measures in prediction of total and cause-specific mortality. *J Epidemiol Community Health* 2016;70:90-6. doi:10.1136/jech-2014-205257
51 Dolan CM, Kraemer H, Browner W, Ensrud K, Kelsey JL. Associations between body composition, anthropometry, and mortality in women aged 65 years and older. *Am J Public Health* 2007;97:913-8. doi:10.2105/AJPH.2005.084178
52 Folsom AR, Kushi LH, Anderson KE, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. *Arch Intern Med* 2000;160:2117-28. doi:10.1001/archinte.160.14.2117
53 Grant JF, Chittleborough CR, Shi Z, Taylor AW. The association between A Body Shape Index and mortality: Results from an Australian cohort. *PLoS One* 2017;12:e0181244. doi:10.1371/journal.pone.0181244
54 Guallar-Castillón P, Balboa-Castillo T, López-García E, et al. BMI, waist circumference, and mortality according to health status in the older adult population of Spain. *Obesity (Silver Spring)* 2009;17:2232-8. doi:10.1038/oby.2009.115
55 He S, Zheng Y, Wang H, Chen X. Assessing the relationship between a body shape index and mortality in a group of middle-aged men. *Clin Nutr* 2017;36:1355-9. doi:10.1016/j.clnu.2016.09.003
56 Heitmann BL, Frederiksen P. Thigh circumference and risk of heart disease and premature death: prospective cohort study. *BMJ* 2009;339:b3292. doi:10.1136/bmj.b3292
57 Heitmann BL, Frederiksen P, Lissner L. Hip circumference and cardiovascular morbidity and mortality in men and women. *Obes Res* 2004;12:482-7. doi:10.1038/oby.2004.54
58 Hotchkiss JW, Davies CA, Leyland AH. Adiposity has differing associations with incident coronary heart disease and mortality in the Scottish population: cross-sectional surveys with follow-up. *Int J Obes (Lond)* 2013;37:732-9. doi:10.1038/ijo.2012.102
59 Howell CR, Mehta T, Ejima K, Ness KK, Cherrington A, Fontaine KR. Body Composition and Mortality in Mexican American Adults: Results

from the National Health and Nutrition Examination Survey. *Obesity (Silver Spring)* 2018;26:1372-80. doi:10.1002/oby.22251
60 Hu H, Wang J, Han X, et al. BMI, Waist Circumference and All-Cause Mortality in a Middle-Aged and Elderly Chinese Population. *J Nutr Health Aging* 2018;22:975-81. doi:10.1007/s12603-018-1047-z
61 Jacobs EJ, Newton CC, Wang Y, et al. Waist circumference and all-cause mortality in a large US cohort. *Arch Intern Med* 2010;170:1293-301. doi:10.1001/archinternmed.2010.201
62 Janssen I, Katzmarzyk PT, Ross R. Body mass index is inversely related to mortality in older people after adjustment for waist circumference. *J Am Geriatr Soc* 2005;53:2112-8. doi:10.1111/j.1532-5415.2005.00505.x
63 Kahn HS, Bullard KM, Barker LE, Imperatore G. Differences between adiposity indicators for predicting all-cause mortality in a representative sample of United States non-elderly adults. *PLoS One* 2012;7:e50428. doi:10.1371/journal.pone.0050428
64 Kalmijn S, Curb JD, Rodriguez BL, Yano K, Abbott RD. The association of body weight and anthropometry with mortality in elderly men: the Honolulu Heart Program. *Int J Obes Relat Metab Disord* 1999;23:395-402. doi:10.1038/sj.ijo.0800832
65 Katzmarzyk PT, Mire E, Bray GA, Greenway FL, Heymsfield SB, Bouchard C. Anthropometric markers of obesity and mortality in white and African American adults: the pennington center longitudinal study. *Obesity (Silver Spring)* 2013;21:1070-5. doi:10.1002/oby.20151
66 Klingberg S, Mehlig K, Lanfer A, Björkelund C, Heitmann BL, Lissner L. Increase in waist circumference over 6 years predicts subsequent cardiovascular disease and total mortality in nordic women. *Obesity (Silver Spring)* 2015;23:2123-30. doi:10.1002/oby.21203
67 Koster A, Leitzmann MF, Schatzkin A, et al. Waist circumference and mortality. *Am J Epidemiol* 2008;167:1465-75. doi:10.1093/aje/kwn079
68 Krakauer NY, Krakauer JC. A new body shape index predicts mortality hazard independently of body mass index. *PLoS One* 2012;7:e39504. doi:10.1371/journal.pone.0039504
69 Krakauer NY, Krakauer JC. Dynamic association of mortality hazard with body shape. *PLoS One* 2014;9:e88793. doi:10.1371/journal.pone.0088793
70 Lahmann PH, Lissner L, Gullberg B, Berglund G. A prospective study of adiposity and all-cause mortality: the Malmö Diet and Cancer Study. *Obes Res* 2002;10:361-9. doi:10.1038/oby.2002.50
71 Lanfer A, Mehlig K, Heitmann BL, Lissner L. Does change in hip circumference predict cardiovascular disease and overall mortality in Danish and Swedish women?*Obesity (Silver Spring)* 2014;22:957-63. doi:10.1002/oby.20604
72 Laukkanen JA, Rauramaa R, Salonen JT, Kurl S. The predictive value of cardiorespiratory fitness combined with coronary risk evaluation and the risk of cardiovascular and all-cause death. *J Intern Med* 2007;262:263-72. doi:10.1111/j.1365-2796.2007.01807.x
73 Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr* 1999;69:373-80. doi:10.1093/ajcn/69.3.373
74 Lee JSW, Auyeung TW, Kwok T, Li M, Leung J, Woo J. Survival benefit of abdominal adiposity: a 6-year follow-up study with Dual X-ray absorptiometry in 3,978 older adults. *Age (Dordr)* 2012;34:597-608. doi:10.1007/s11357-011-9272-y
75 Lindqvist P, Andersson K, Sundh V, Lissner L, Björkelund C, Bengtsson C. Concurrent and separate effects of body mass index and waist-to-hip ratio on 24-year mortality in the Population Study of Women in Gothenburg: evidence of age-dependency. *Eur J Epidemiol* 2006;21:789-94. doi:10.1007/s10654-006-9074-1
76 Lissner L, Björkelund C, Heitmann BL, Seidell JC, Bengtsson C. Larger hip circumference independently predicts health and longevity in a Swedish female cohort. *Obes Res* 2001;9:644-6. doi:10.1038/oby.2001.85
77 Martinez-Gomez D, Guallar-Castillón P, Hallal PC, Lopez-Garcia E, Rodríguez-Artalejo F. Nonexercise cardiorespiratory fitness and mortality in older adults. *Med Sci Sports Exerc* 2015;47:568-74. doi:10.1249/MSS.0000000000000435
78 Mason C, Craig CL, Katzmarzyk PT. Influence of central and extremity circumferences on all-cause mortality in men and women. *Obesity (Silver Spring)* 2008;16:2690-5. doi:10.1038/oby.2008.438
79 McNeely MJ, Shofer JB, Leonetti DL, Fujimoto WY, Boyko EJ. Associations among visceral fat, all-cause mortality, and obesity-related mortality in Japanese Americans. *Diabetes Care* 2012;35:296-8. doi:10.2337/dc11-1193
80 Moliner-Urdiales D, Artero EG, Lee DC, España-Romero V, Sui X, Blair SN. Body adiposity index and all-cause and cardiovascular disease mortality in men. *Obesity (Silver Spring)* 2013;21:1870-6. doi:10.1002/oby.20399
81 Park Y, Kim NH, Kwon TY, Kim SG. A novel adiposity index as an integrated predictor of cardiometabolic disease morbidity and mortality. *Sci Rep* 2018;8:16753. doi:10.1038/s41598-018-35073-4
82 Petursson H, Sigurdsson JA, Bengtsson C, Nilsen TI, Getz L. Body configuration as a predictor of mortality: comparison of five anthropometric measures in a 12 year follow-up of the Norwegian HUNT 2 study. *PLoS One* 2011;6:e26621. doi:10.1371/journal.pone.0026621
83 Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;359:2105-20. doi:10.1056/NEJMoa0801891
84 Price GM, Uauy R, Breeze E, Bulpitt CJ, Fletcher AE. Weight, shape, and mortality risk in older persons: elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. *Am J Clin Nutr* 2006;84:449-60. doi:10.1093/ajcn/84.2.449
85 Pujilestari CU, Nyström L, Norberg M, Ng N. Waist Circumference and All-Cause Mortality among Older Adults in Rural Indonesia. *Int J Environ Res Public Health* 2019;16:116. doi:10.3390/ijerph16010116
86 Reis JP, Macera CA, Araneta MR, Lindsay SP, Marshall SJ, Wingard DL. Comparison of overall obesity and body fat distribution in predicting risk of mortality. *Obesity (Silver Spring)* 2009;17:1232-9. doi:10.1038/oby.2008.664
87 Rost S, Freuer D, Peters A, et al. New indexes of body fat distribution and sex-specific risk of total and cause-specific mortality: a prospective cohort study. *BMC Public Health* 2018;18:427. doi:10.1186/s12889-018-5350-8
88 Saito I, Kokubo Y, Kiyohara Y, et al. Prospective study on waist circumference and risk of all-cause and cardiovascular mortality: pooled analysis of Japanese community-based studies. *Circ J* 2012;76:2867-74. doi:10.1253/circj.CJ-11-1259
89 Sardarinia M, Ansari R, Azizi F, Hadaegh F, Bozorgmanesh M. Mortality prediction of a body shape index versus traditional anthropometric measures in an Iranian population: Tehran Lipid and Glucose Study. *Nutrition* 2017;33:105-12. doi:10.1016/j.nut.2016.05.004
90 Sato Y, Fujimoto S, Konta T, et al. Body shape index: Sex-specific differences in predictive power for all-cause mortality in the Japanese population. *PLoS One* 2017;12:e0177779. doi:10.1371/journal.pone.0177779
91 Schneider HJ, Friedrich N, Klotsche J, et al. The predictive value of different measures of obesity for incident cardiovascular events and mortality. *J Clin Endocrinol Metab* 2010;95:1777-85. doi:10.1210/jc.2009-1584
92 Simpson JA, MacInnis RJ, Peeters A, Hopper JL, Giles GG, English DR. A comparison of adiposity measures as predictors of all-cause mortality: the Melbourne Collaborative Cohort Study. *Obesity (Silver Spring)* 2007;15:994-1003. doi:10.1038/oby.2007.622
93 Singh K, Patel SA, Biswas S, et al. Multimorbidity in South Asian adults: prevalence, risk factors and mortality. *J Public Health (Oxf)* 2019;41:80-9. doi:10.1093/pubmed/fdy017
94 Srikanthan P, Seeman TE, Karlamangla AS. Waist-hip-ratio as a predictor of all-cause mortality in high-functioning older adults. *Ann Epidemiol* 2009;19:724-31. doi:10.1016/j.annepidem.2009.05.003
95 Staiano AE, Reeder BA, Elliott S, et al. Body mass index versus waist circumference as predictors of mortality in Canadian adults. *Int J Obes (Lond)* 2012;36:1450-4. doi:10.1038/ijo.2011.268
96 Thomas F, Pannier B, Bean K, Danchin N. Waist circumference and mortality: impact of associated risk factors. *Diabetes Metab* 2011;37:33-8. doi:10.1016/j.diabet.2010.07.003
97 Thomson CA, Garcia DO, Wertheim BC, et al. Body shape, adiposity index, and mortality in postmenopausal women: Findings from the Women's Health Initiative. *Obesity (Silver Spring)* 2016;24:1061-9. doi:10.1002/oby.21461
98 Tice JA, Kanaya A, Hue T, et al. Risk factors for mortality in middle-aged women. *Arch Intern Med* 2006;166:2469-77. doi:10.1001/archinte.166.22.2469
99 Visscher TL, Seidell JC, Molarius A, van der Kuip D, Hofman A, Witteman JC. A comparison of body mass index, waist-hip ratio and waist circumference as predictors of all-cause mortality among the elderly: the Rotterdam study. *Int J Obes Relat Metab Disord* 2001;25:1730-5. doi:10.1038/sj.ijo.0801787
100 Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Decreased muscle mass and increased central adiposity are independently related to mortality in older men. *Am J Clin Nutr* 2007;86:1339-46. doi:10.1093/ajcn/86.5.1339
101 Welborn TA, Dhaliwal SS. Preferred clinical measures of central obesity for predicting mortality. *Eur J Clin Nutr* 2007;61:1373-9. doi:10.1038/sj.ejcn.1602656
102 Wu L-W, Lin Y-Y, Kao T-W, et al. Mid-arm circumference and all-cause, cardiovascular, and cancer mortality among obese and non-obese US adults: the national health and nutrition examination survey III. *Sci Rep* 2017;7:2302. doi:10.1038/s41598-017-02663-7
103 Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. *Circulation* 2008;117:1658-67. doi:10.1161/CIRCULATIONAHA.107.739714

104 Zhao Q, Zmuda JM, Kuipers AL, et al. Greater skeletal muscle fat infiltration is associated with higher all-cause mortality among men of African ancestry. *Age Ageing* 2016;45:529-34. doi:10.1093/ageing/afw062
105 Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci* 2017;13:851-63. doi:10.5114/aoms.2016.58928
106 Marseglia L, Manti S, D'Angelo G, et al. Oxidative stress in obesity: a critical component in human diseases. *Int J Mol Sci* 2014;16:378-400. doi:10.3390/ijms16010378
107 Ye J. Mechanisms of insulin resistance in obesity. *Front Med* 2013;7:14-24. doi:10.1007/s11684-013-0262-6
108 Jayedi A, Rashidy-Pour A, Khorshidi M, Shab-Bidar S. Body mass index, abdominal adiposity, weight gain and risk of developing hypertension: a systematic review and dose-response meta-analysis of more than 2.3 million participants. *Obes Rev* 2018;19:654-67. doi:10.1111/obr.12656
109 Klop B, Elte JW, Cabezas MC. Dyslipidemia in obesity: mechanisms and potential targets. *Nutrients* 2013;5:1218-40. doi:10.3390/nu5041218
110 Engin A. Endothelial Dysfunction in Obesity. *Adv Exp Med Biol* 2017;960:345-79. doi:10.1007/978-3-319-48382-5_15
111 Poirier P, Giles TD, Bray GA, et al, American Heart Association, Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2006;113:898-918. doi:10.1161/CIRCULATIONAHA.106.171016
112 Kyrgiou M, Kalliala I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. *BMJ* 2017;356:j477. doi:10.1136/bmj.j477
113 Jayedi A, Zargar M. Body mass index and risk of end-stage renal disease: a systematic review and dose-response meta-analysis. *Journal of Nutritional Sciences and Dietetics* 2018;4.
114 Strazzullo P, D'Elia L, Cairella G, Garbagnati F, Cappuccio FP, Scalfi L. Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. *Stroke* 2010;41:e418-26. doi:10.1161/STROKEAHA.109.576967
115 Chooi YC, Ding C, Magkos F. The epidemiology of obesity. *Metabolism* 2019;92:6-10. doi:10.1016/j.metabol.2018.09.005
116 Nevill AM, Stewart AD, Olds T, Holder R. Relationship between adiposity and body size reveals limitations of BMI. *Am J Phys Anthropol* 2006;129:151-6. doi:10.1002/ajpa.20262
117 Bigaard J, Frederiksen K, Tjønneland A, et al. Body fat and fat-free mass and all-cause mortality. *Obes Res* 2004;12:1042-9. doi:10.1038/oby.2004.131
118 Ohlson L-O, Larsson B, Svärdsudd K, et al. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 1985;34:1055-8. doi:10.2337/diab.34.10.1055
119 Rexrode KM, Carey VJ, Hennekens CH, et al. Abdominal adiposity and coronary heart disease in women. *JAMA* 1998;280:1843-8. doi:10.1001/jama.280.21.1843
120 Després JP. Cardiovascular disease under the influence of excess visceral fat. *Crit Pathw Cardiol* 2007;6:51-9. doi:10.1097/HPC.0b013e318057d4c9
121 Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation* 2007;116:39-48. doi:10.1161/CIRCULATIONAHA.106.675355
122 Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. *BMJ* 1995;311:158-61. doi:10.1136/bmj.311.6998.158
123 Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. *Arch Intern Med* 2002;162:2074-9. doi:10.1001/archinte.162.18.2074
124 Bosomworth NJ. Normal-weight central obesity: Unique hazard of the toxic waist. *Can Fam Physician* 2019;65:399-408.
125 Sahakyan KR, Somers VK, Rodriguez-Escudero JP, et al. Normal-Weight Central Obesity: Implications for Total and Cardiovascular Mortality. *Ann Intern Med* 2015;163:827-35. doi:10.7326/M14-2525
126 Bouchi R, Asakawa M, Ohara N, et al. Indirect measure of visceral adiposity 'A Body Shape Index' (ABSI) is associated with arterial stiffness in patients with type 2 diabetes. *BMJ Open Diabetes Res Care* 2016;4:e000188. doi:10.1136/bmjdrc-2015-000188
127 Krakauer NY, Krakauer JC. Untangling Waist Circumference and Hip Circumference from Body Mass Index with a Body Shape Index, Hip Index, and Anthropometric Risk Indicator. *Metab Syndr Relat Disord* 2018;16:160-5. doi:10.1089/met.2017.0166
128 Identification EPot. *Overweight To, Adults Oi, et al. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report.* National Institutes of Health, National Heart, Lung, and Blood Institute, 1998.
129 Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006;23:469-80. doi:10.1111/j.1464-5491.2006.01858.x
130 Balkau B, Charles MA, European Group for the Study of Insulin Resistance (EGIR). Comment on the provisional report from the WHO consultation. *Diabet Med* 1999;16:442-3. doi:10.1046/j.1464-5491.1999.00059.x
131 Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-53. doi:10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S
132 Ashwell M, Gibson S. A proposal for a primary screening tool: 'Keep your waist circumference to less than half your height'. *BMC Med* 2014;12:207. doi:10.1186/s12916-014-0207-1
133 Ashwell M, Hsieh SD. Six reasons why the waist-to-height ratio is a rapid and effective global indicator for health risks of obesity and how its use could simplify the international public health message on obesity. *Int J Food Sci Nutr* 2005;56:303-7. doi:10.1080/09637480500195066
134 Ashwell M, Lejeune S, McPherson K. Ratio of waist circumference to height may be better indicator of need for weight management. *BMJ* 1996;312:377. doi:10.1136/bmj.312.7027.377
135 Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0·5 could be a suitable global boundary value. *Nutr Res Rev* 2010;23:247-69. doi:10.1017/S0954422410000144
136 Snijder MB, van Dam RM, Visser M, Seidell JC. What aspects of body fat are particularly hazardous and how do we measure them?*Int J Epidemiol* 2006;35:83-92. doi:10.1093/ije/dyi253
137 Cameron AJ, Söderberg S, Magliano DJ. Comment on 'General and abdominal obesity parameters and their combination in relation to mortality: a systematic review and meta-regression analysis'. *Eur J Clin Nutr* 2014;68:140. doi:10.1038/ejcn.2013.187
138 Flegal KM, Graubard BI, Williamson DF, Cooper RS. Reverse causation and illness-related weight loss in observational studies of body weight and mortality. *Am J Epidemiol* 2011;173:1-9. doi:10.1093/aje/kwq341
139 Flegal KM, Graubard BI, Williamson DF, Gail MH. Impact of smoking and preexisting illness on estimates of the fractions of deaths associated with underweight, overweight, and obesity in the US population. *Am J Epidemiol* 2007;166:975-82. doi:10.1093/aje/kwm152
140 Sun Y, Liu B, Snetselaar LG, et al. Association of Normal-Weight Central Obesity With All-Cause and Cause-Specific Mortality Among Postmenopausal Women. *JAMA Netw Open* 2019;2:e197337. doi:10.1001/jamanetworkopen.2019.7337
141 Bender R, Jöckel K-H, Trautner C, Spraul M, Berger M. Effect of age on excess mortality in obesity. *JAMA* 1999;281:1498-504. doi:10.1001/jama.281.16.1498
142 Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. *N Engl J Med* 1998;338:1-7. doi:10.1056/NEJM199801013380101

Web appendix: Appendix 1

No commercial reuse: See rights and reprints http://www.bmj.com/permissions Subscribe: http://www.bmj.com/subscribe