Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study

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Summary

Background **Obesity is a major risk factor for cardiovascular disease, but the most predictive measure for different ethnic populations is not clear. We aimed to assess whether markers of obesity, especially waist-to-hip ratio, would be stronger indicators of myocardial infarction than body-mass index (BMI), the conventional measure.**

Methods **We did a standardised case-control study of acute myocardial infarction with 27 098 participants in 52 countries (12 461 cases and 14 637 controls) representing several major ethnic groups. We assessed the relation between BMI, waist and hip circumferences, and waist-to-hip ratio to myocardial infarction overall and for each group.**

Findings **BMI showed a modest and graded association with myocardial infarction (OR 1·44, 95% CI 1·32–1·57 top quintile vs bottom quintile before adjustment), which was substantially reduced after adjustment for waist-to-hip ratio (1·12, 1·03–1·22), and non-significant after adjustment for other risk factors (0·98, 0·88–1·09). For waist-to-hip ratio, the odds ratios for every successive quintile were significantly greater than that of the previous one (2nd quintile: 1·15, 1·05–1·26; 3rd quintile: 1·39; 1·28–1·52; 4th quintile: 1·90, 1·74–2·07; and 5th quintiles: 2·52, 2·31–2·74 [adjusted for age, sex, region, and smoking]). Waist (adjusted OR 1·77; 1·59–1·97) and hip (0·73; 0·66–0·80) circumferences were both highly significant after adjustment for BMI ($p<0·0001$ top *vs* bottom quintiles). Waist-to-hip ratio and waist and hip circumferences were closely ($p<0·0001$) associated with risk of myocardial infarction even after adjustment for other risk factors (ORs for top quintile *vs* lowest quintiles were 1·75, 1·33, and 0·76, respectively). The population-attributable risks of myocardial infarction for increased waist-to-hip ratio in the top two quintiles was 24·3% (95% CI 22·5–26·2) compared with only 7·7% (6·0–10·0) for the top two quintiles of BMI.**

Interpretation **Waist-to-hip ratio shows a graded and highly significant association with myocardial infarction risk worldwide. Redefinition of obesity based on waist-to-hip ratio instead of BMI increases the estimate of myocardial infarction attributable to obesity in most ethnic groups.**

Introduction

Obesity increases the risk of cardiovascular diseases and diabetes,[1,2] but these data are derived mainly from high-income countries. Although most of the global burden of cardiovascular disease is in developing countries, few data are available for the effect of obesity in these populations.[3] Further, we do not know the measure of obesity (body-mass index [BMI], waist or hip circumferences, or waist-to-hip ratio) that shows the strongest relation to the risk of such disease and whether these measures are similar across different ethnic groups, in men and women, and at different ages.[4] Previous studies provided conflicting results, possibly because of the modest number of cardiovascular events (a few hundred).[5–9]

On the basis of two previous smaller studies,[10,11] we had postulated that markers of central obesity (especially the waist-to-hip ratio) would be more strongly related to the risk of myocardial infarction than BMI (the conventional measure). We aimed to investigate the relation of BMI, waist and hip circumferences, and waist-to-hip ratio to the risk of myocardial infarction using data from the INTERHEART study,[12,13] of about 15 000 cases and a similar number of controls representing many ethnic groups.

Methods

Participants

We did a standardised case-control study of 15 152 cases of first myocardial infarction, and 14 820 age-matched and sex-matched controls. Details have been published previously.[5] Consecutive cases of first myocardial infarction presenting within 24 h of symptom onset were eligible. All consenting cases without cardiogenic shock or history of major chronic diseases were included. At least one age-matched (±5 years) and sex-matched control (without a history of cardiovascular disease) was recruited per case by use of specific criteria.[5] The first control per case was an attendant or relative of a patient from a non-cardiac ward or an unrelated (not first-degree relative) attendant of another cardiac patient. A second control per case was selected from those at the same centre with illnesses not obviously related to coronary heart disease or its risk factors.

Study participants were recruited from 262 centres in 52 countries in Asia, Europe, the middle east, Africa, Australia, North America, and South America.

Of the cases, 1531 were excluded because they had unstable angina, 205 did not have a confirmed myocardial infarction, 695 had a previous myocardial infarction, and 260 had insufficient data. 74 controls were excluded because of insufficient data, and 109 had a previous history of myocardial infarction. Therefore, 12 461 cases and 14 637 controls were available for study, although weight or height was missing in 544 participants (2%), and waist or hip measurements were missing in 959 participants (3·5%).

Procedures

Structured questionnaires were administered and physical examinations were done in the same way in cases and controls. Information was obtained about demographic factors, socioeconomic status, lifestyle, risk factors, and personal and family history of cardiovascular disease.[5] Waist and hip circumferences were measured with a non-stretchable standard tape measure attached to a spring scale at a tension of 750 g. Waist circumference was measured over the unclothed abdomen at the narrowest point between the costal margin and iliac crest, and hip circumference was measured over light clothing at the level of the widest diameter around the buttocks. Both weight and height were measured with standardised protocols. Details of blood sampling, storage, transportation, and analyses have been published previously.[10]

All data were transferred to the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Canada. The protocol was approved by the ethics committee at each of the participating centres and all participants provided written informed consent.

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Statistical methods

Univariate associations were explored with frequency tables and Pearson's χ^2 tests for independent proportions. For comparisons of prevalence of obesity across subgroups (eg, by region or ethnicity), the potential differences in age structure of the populations were accounted for by direct standardisation of the frequencies to the overall INTERHEART age distribution with a five level age stratification.[14] Continuous variables were summarised by means or medians and were compared with t tests or non-parametric tests, dependent on their distribution. For comparison of means across subgroups, values were adjusted for age and sex with analysis of covariance (ANCOVA) models. Sex-specific quantile values in controls were used to categorise continuous variables. Unconditional logistic regression with adjustment for matching factors was used to control for confounding by other risk factors. Results from unconditional analyses were similar to those from conditional and mixed effect models analyses (<5% variation). Analyses adjusted for the other eight INTERHEART risk factors (smoking, apolipoproteins B and A [ApoB/ApoA ratio], history of hypertension, history of diabetes, diet, activity, alcohol use, and psychosocial variables) are also presented.

Population-attributable risks and their 95% CI were calculated by a method based on unconditional logistic regression,[15] with the Interactive Risk Attributable Program (US National Cancer Institute, 2002).[16]

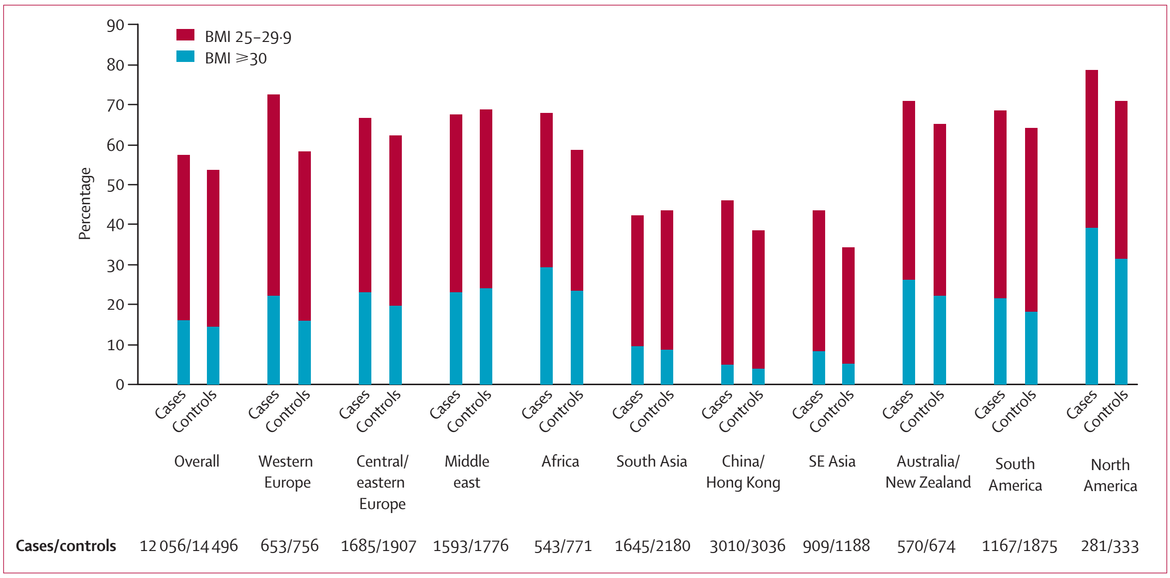

Figure 1: **Proportion of cases and controls who are obese or overweight**
W Eur=Western Europe, C/E Eur=Central or eastern Europe, MEC=Middle east, Afr=Africa, S=South, Chn=China, HK=Hong Kong, ANZ=Australia and New Zealand, Amer=America, N=North.

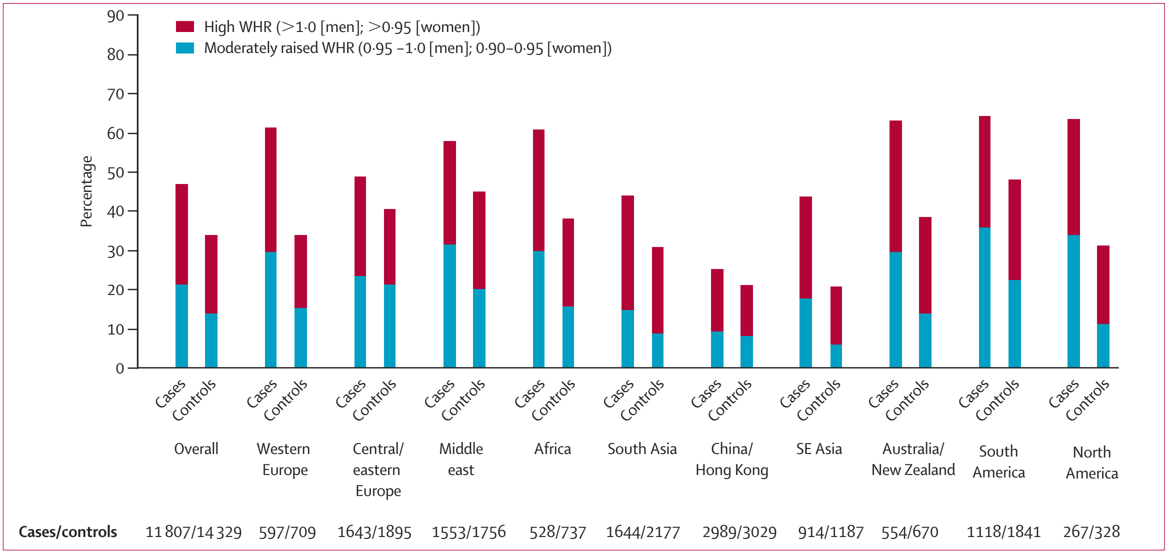

Figure 2: **Percentage (age-adjusted) of cases and controls with abdominal obesity (waist-to-hip ratio) overall and by region**
WHR=waist-to-hip ratio.

The relative importance of various measures of obesity in prediction of myocardial infarction was assessed in several different ways. First, we compared the odds ratios (ORs) across various quintiles; second, we estimated the OR for 1 SD change in the measure, (using both overall and subgroup specific SD); third, we

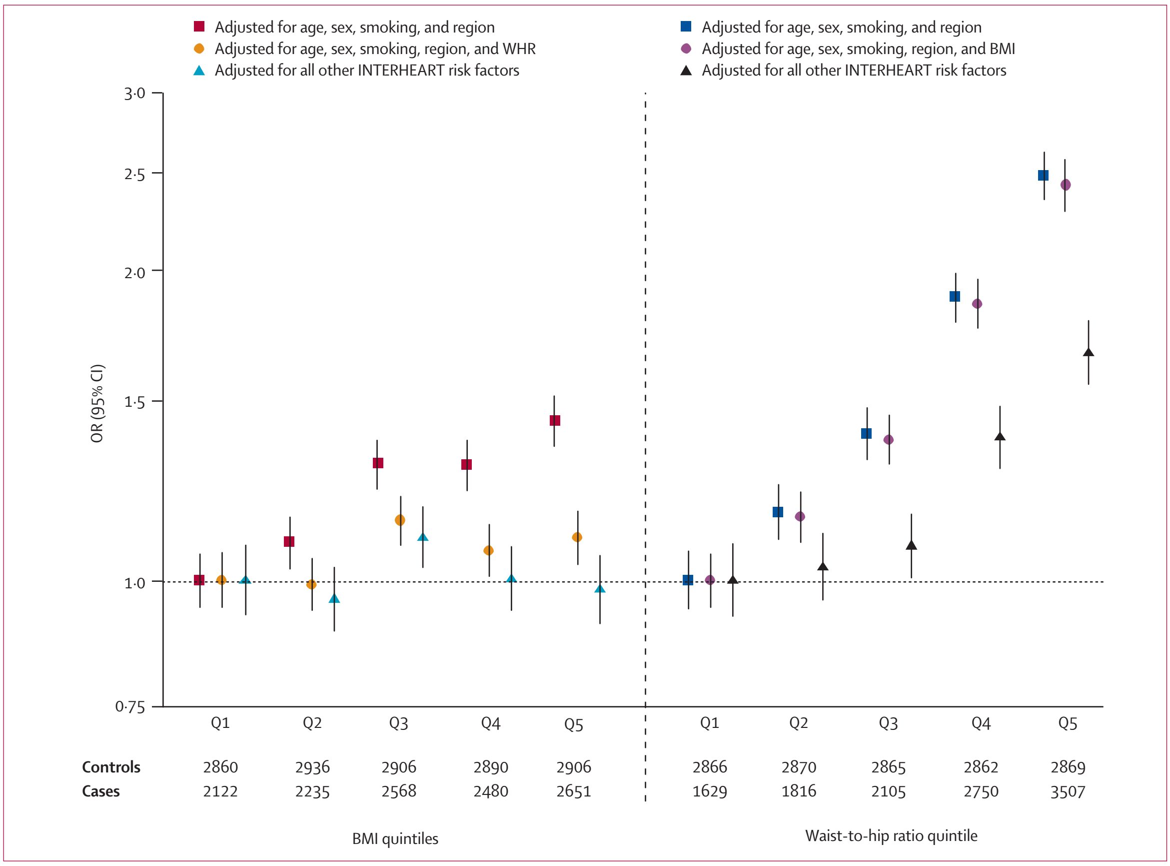

Figure 3: **Association of BMI and waist-to-hip ratio with myocardial infarction risk**
Vertical bars=95% CIs.

compared the receiver-operator-curves in relation to myocardial infarction for all measures;[17] fourth, we calculated the incremental (likelihood ratio) χ^2 values for every measure when added to other measures.[18] Where categorical analyses were used and it was deemed useful to compare various levels with each other, as opposed to the usual situation of only comparisons to the reference category being valid, we used the quasi-variance approach of Firth and de Menezes[19] to remove total dependence of confidence interval width on the reference category. All statistical tests were two-sided. Statistical analyses and graphics were produced with the SAS system version 9.1 and S-Plus version 6.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit this manuscript for publication.

Results

A total of 27 098 participants (12 461 cases and 14 637 age-matched and sex-matched controls) were included in these analyses. The distribution of various risk factors between cases and controls has been reported previously[5] (webtable 1); here we focus only on measures related to obesity. There was no significant difference in height between cases and controls. The mean BMI in controls was 25·8 kg/m², (95% CI; 25·8–25·9); 25·6 kg/m² (25·5–25·7) in men and 26·5 kg/m² (26·4–26·7) in women (webtable 2).

See Lancet Online for webtable 1

See Lancet Online for webtable 2

The mean BMI was lowest in south Asia (24·9), China (24·4), and southeast Asia (24·0); intermediate in central and eastern Europe (26·7), South America (26·7), Africa (26·7), and western Europe (26·5); and highest in North America (27·7), the middle east (27·4), and Australia and New Zealand (27·0). Striking variations could also be seen in the proportion of those with obesity (BMI >30 kg/m²) or overweight (>25 kg/m²) in the various regions (figure 1). Data for waist-to-hip ratio in the various regions indicated a different pattern compared with BMI (webtable 2). Mean waist-to-hip ratio was lowest in China (0·88), intermediate in North America (0·90), southeast Asia (0·89), Europe (0·91), Africa (0·92), and south Asian countries (0·91); but highest in the middle east (0·93) and South America (0·94). In women, the highest BMI and waist-to-hip ratio were recorded in the middle east (BMI of 29·5, waist-to-hip ratio of 0·92). By contrast, the

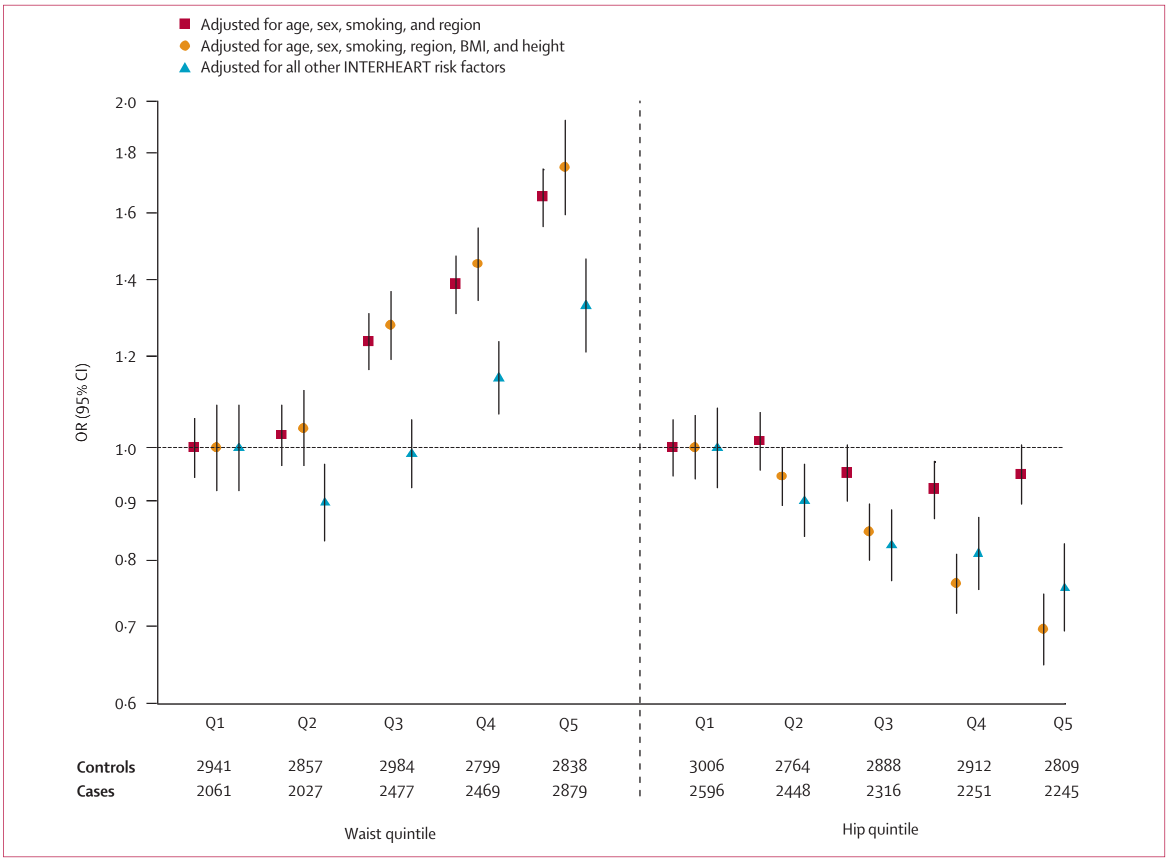

Figure 4: **Risk of MI associated with increasing waist circumference and hip circumference**
Vertical bars=95% CIs.

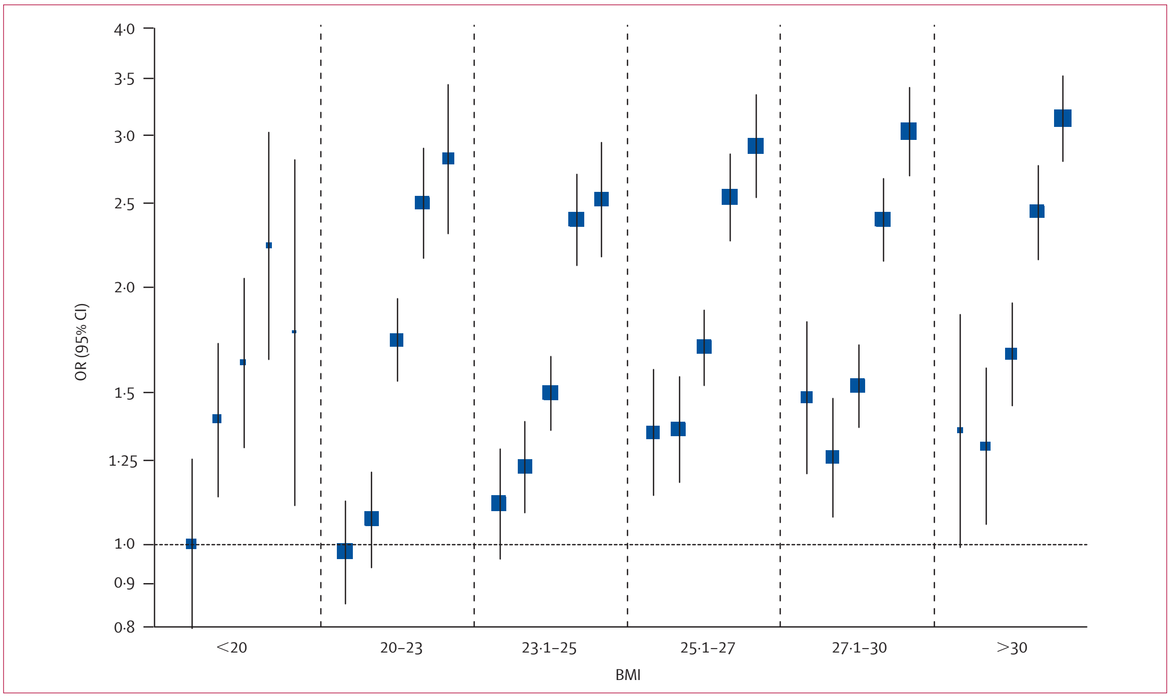

Figure 5: **Association of waist-to-hip ratio within BMI categories with myocardial infarction risk**

highest BMI in men was in North America (28·3) and the highest waist-to-hip ratio was in South America (0·96). Thus, dependent on whether BMI or waist-to-hip ratio is used, there is considerable difference in the proportion regarded as obese in different regions (figures 1 and 2). BMI was only slightly higher in myocardial infarction cases than in controls, with no difference in the middle east and south Asia (figure 1). By contrast, cases had a strikingly higher waist-to-hip ratio than controls, an observation consistent in all regions of the world.

With increasing BMI values, the risk of myocardial infarction increased. Patients in the highest quintile (BMI >28·2 in women or >28·6 in men) had a 1·44-fold (95% CI 1·32–1·57) increased risk of myocardial infarction (p<0·001) compared with those with a BMI in the lowest quintile (≤22·7 in women or ≤22·5 in men). However, this relation diminished substantially after adjustment for waist-to-hip ratio (OR 1·12, 95% CI 1·03–1·22), and disappeared after adjustment for the other eight risk factors (0·98, 0·88–1·09) (figure 3).

Waist circumference was strongly related to myocardial infarction risk (figure 4). This relation was continuous and persisted even after adjustment for BMI and height. The OR for the highest quintile (>97·4 cm women and >99·0 cm males) compared to the lowest quintile (<75·8cm in women and <80·5 cm in men) was 1·77 (1·59–1·97; p<0·0001). After adjustment for the other risk factors, this association was diminished (1·33, 1·16–1·53) but still highly significant (p<0·0001).

A trend toward lower risk of myocardial infarction was noted as hip circumference increased. This trend was highly significant after adjustment for BMI and height. Compared with the lowest quintile (≤90 cm in women and ≤89 cm in men), the highest quintile of hip

	Odds Ratio (95% CI)			Odds Ratio (95% CI)		
	1 SD	Adjusted for age, sex, and region	Additionally adjusted for WHR or BMI	1 SD (women/men)	Women	Men
Measure (units)						
BMI (kg/m^2)	4·15	1·10 (1·07–1·13)	1·02 (0·99–1·04)*	4·70/3·89	1·04 (0·98–1·09)*	1·00 (0·97–1·04)*
Waist circumference (cm)	12·08	1·19 (1·16–1·22)	1·25 (1·21–1·30)†	12·97/11·58	1·40 (1·30–1·51)†	1·19 (1·14–1·24)†
Hip circumference (cm)	10·96	0·96 (0·94–0·99)	0·87 (0·84–0·89)†	12·18/10·36	0·92 (0·86–0·99)†	0·85 (0·82–0·89)†
Waist-to-hip ratio	0·085	1·37 (1·34–1·41)	1·37 (1·33–1·40)†	0·089/0·078	1·34 (1·27–1·42)†	1·35 (1·31–1·40)†
Waist-to-height	0·072	1·19 (1·16–1·22)	1·24 (1·20–1·29)†	0·082/0·066	1·39 (1·29–1·50)†	1·18 (1·13–1·23)†

BMI=body-mass index. WHR=waist-to-hip ratio. Odds ratios by sex are adjusted for age, region, and BMI or WHR as appropriate. *Adjusted for WHR. †Adjusted for BMI and height.

Table 1: **Comparative effect of 1 standard deviation increase in a specific measure of obesity in the overall population and separately in men and women**

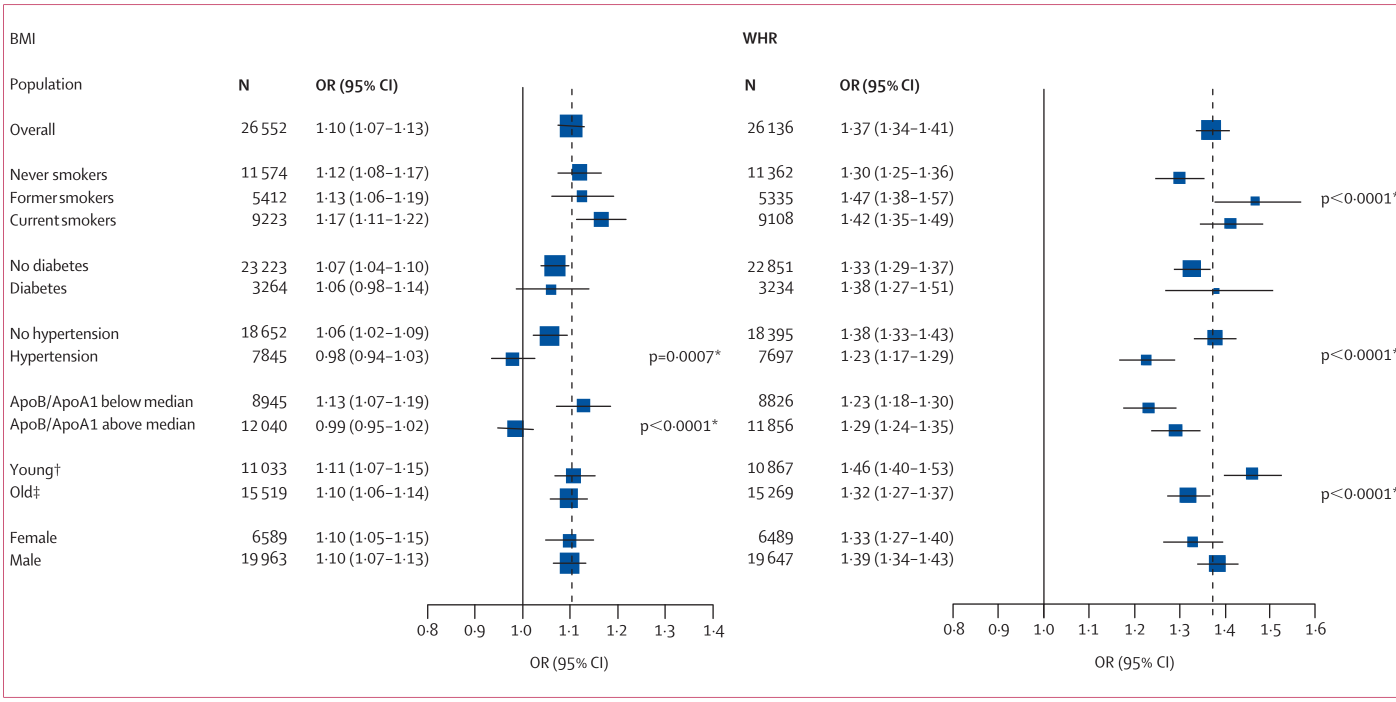

Figure 6: **Odds ratio for myocardial infarction for 1 SD increase**
*p values are for heterogeneity between the subgroup.

circumference (>109·8 cm in women and >105 cm in men) was associated with an OR for myocardial infarction of 0·73 (0·66–0·80; p<0·0001). This association was unchanged after adjustment for the other eight risk factors (0·76, 0·67–0·86).

The risk of myocardial infarction rose progressively with increasing values for waist-to-hip ratio, with no evidence of a threshold (figure 3). The increased odds ratio with successive quintiles was significantly greater than the odds ratio associated with the previous one (p<0·0001), even after adjustment for BMI (figure 4) and other risk factors (highest *vs* lowest quintiles, 1·75, 1·57–1·95; p<0·0001). This relation was consistent in men and women. These relations were much stronger than that between BMI and myocardial infarction. For example, those in the highest quintile had a 2·52-fold increase in odds (2·31–2·74, p<0·0001) compared with those in the lowest quintile. This continuous relation between waist-to-hip ratio and myocardial infarction risk persists within various subgroups of individuals categorised by BMI index, so that increasing waist-to-hip ratio is a predictor of myocardial infarction even in those regarded as very lean (BMI <20) and in those regarded as being of ideal weight (⩾20 to <25), overweight (>25), or obese (>30) (figure 5).

The OR associated with 1 SD increase in waist-to-hip ratio was the strongest, whereas that of BMI was the weakest (table 1). Waist circumference was intermediate between BMI and waist-to-hip ratio. Increasing values of hip was slightly protective. Further analyses, controlling for BMI and height considerably strengthened the association of both waist (OR 1·25, 95% CI 1·21–1·30) and hip circumferences with myocardial infarction (0·87, 0·84–0·89). Comparing the χ^2 associated with

	BMI (95% CI)*	Waist (95% CI)†	WHR (95%CI)‡
Overall	1·10 (1·07–1·13)	1·19 (1·16–1·22)	1·37 (1·34–1·41)
European	1·14 (1·09–1·20)	1·25 (1·19–1·31)	1·44 (1·36–1·51)
Chinese	1·19 (1·11–1·27)	1·24 (1·16–1·33)	1·08 (1·03–1·14)
South Asian	0·99 (0·93–1·05)	1·03 (0·97–1·10)	1·52 (1·41–1·64)
Other Asian	1·29 (1·17–1·43)	1·58 (1·41–1·78)	2·60 (2·25–3·01)
Arab	1·00 (0·93–1·07)	1·07 (0·99–1·16)	1·43 (1·31–1·57)
Latin American	1·12 (1·04–1·21)	1·20 (1·11–1·29)	1·43 (1·32–1·56)
Black African	1·29 (1·10–1·52)	1·57 (1·31–1·88)	1·36 (1·09–1·69)
Mixed-race African§	1·07 (0·94–1·22)	1·16 (0·99–1·34)	2·25 (1·79–2·84)

BMI=body-mass index. WHR=waist-to-hip ratio. SD is not subgroup specific. *SD=4·15. †SD=12·08. ‡SD=0·085. §Black and white mixed-race in South Africa. Analysis using SD that are specific to each ethnic group leads to similar results for all groups other than Chinese, in whom the OR for BMI decreases considerably to 1·04, and for waist circumference to 1·18, but remains unchanged for WHR.

Table 2: **Increases in odds ratio for myocardial infarction for 1 SD increase in body-mass index, waist circumference, or waist-to-hip ratio in different ethnic groups adjusted for age and sex**

	High waist-to-hip ratio*†§ >0·83 women/>0·9 men			BMI>25†§ (overweight)			BMI>30‡§ (obese)		
	Prev controls	OR¶ (95% CI)	PAR (95%CI)	Prev controls	OR (95% CI)	PAR (95%CI)	Prev controls	OR (95% CI)	PAR (95%CI)
Overall	66·7	1·77 (1·67 to 1·88)	33·7 (31·0 to 36·5)	53·7	1·28 (1·21 to 1·35)	10·8 (8·6 to 13·6)	14·6	1·24 (1·16 to 1·33)	2·8 (2·0 to 4·0)
Female	66·8	1·90 (1·69 to 2·14)	35·9 (30·5 to 41·7)	57·3	1·19 (1·07 to 1·32)	9·3 (5·1 to 16·3)	20·2	1·26 (1·12 to 1·43)	5·4 (3·4 to 8·5)
Male	66·7	1·73 (1·62 to 1·85)	32·1 (29·1 to 35·4)	52·4	1·31 (1·23 to 1·39)	10·9 (8·4 to 14·1)	12·6	1·23 (1·13 to 1·34)	2·01 (1·2 to 3·4)
European	68·4	2·23 (1·98 to 2·51)	44·4 (39·4 to 49·6)	63·3	1·46 (1·31 to 1·61)	16·6 (11·7 to 23·0)	20·7	1·32 (1·17 to 1·48)	5·3 (3·4 to 8·3)
Chinese	53·8	1·18 (1·06 to 1·30)	8·55 (4·6 to 15·4)	37·9	1·33 (1·20 to 1·47)	11·6 (8·4 to 15·8)	4·4	1·16 (0·91 to 1·47)	0·71 (0·16 to 3·15)
South Asian	68·2	1·91 (1·65 to 2·20)	36·8 (30·5 to 43·5)	46·0	1·07 (0·94 to 1·21)	−0·69 (−6·06 to 4·68)	9·7	1·24 (1·01 to 1·52)	1·0 (0·16 to 6·3)
Other Asian	57·0	3·63 (2·91 to 4·52)	58·2 (51·3 to 64·7)	36·7	1·54 (1·27 to 1·86)	14·1 (8·7 to 22·1)	5·7	1·84 (1·28 to 2·64)	4·0 (2·1 to 7·4)
Arabic	78·8	1·47 (1·20 to 1·82)	30·9 (20·6 to 43·4)	72·6	0·99 (0·83 to 1·19)	0·73 (−11·48 to 12·93)	26·3	1·02 (0·86 to 1·22)	−0·80 (−5·41 to 3·81)
Latin American	79·0	2·06 (1·64 to 2·59)	44·3 (34·1 to 55·1)	64·2	1·24 (1·05 to 1·46)	9·8 (3·5 to 24·3)	18·4	1·26 (1·04 to 1·52)	4·4 (1·9 to 9·9)
Black African	66·6	1·94 (1·19 to 3·17)	41·8 (22·5 to 63·9)	60·2	2·33 (1·49 to 3·66)	38·7 (21·7 to 59·0)	22·7	2·23 (1·45 to 3·45)	18·6 (9·6 to 32·8)
Mixed-race African‖	71·0	3·56 (2·27 to 5·58)	63·6 (49·2 to 76·0)	59·3	1·62 (1·16 to 2·27)	18·9 (7·1 to 41·5)	27·8	1·08 (0·75 to 1·55)	−0·76 (−10·73 to 9·20)
Other	72·8	1·85 (0·75 to 4·60)	49·1 (16·7 to 82·3)	62·2	2·13 (0·98 to 4·61)	34·3 (9·4 to 72·4)	21·1	1·95 (0·88 to 4·31)	11·9 (2·4 to 42·9)

Prev=prevalence. PAR=population-attributable risk. BMI=body-mass index. WHR=waist-to-hip ratio. *Upper two-thirds of the distribution. †Overweight. ‡Obese. §Upper two quintiles for WHR had a PAR of 24·3% versus 7·7% for same quintiles for BMI. ¶Odds ratio for 2nd tertile versus 1st is 1·36, and for 3rd versus 1st is 2·24. OR for top two tertiles versus lowest tertile is 1·77. ‖Black and white mixed-race in South Africa.

Table 3: **Odds ratios and population-attributable risk of myocardial infarction for raised waist-to-hip ratio or body-mass index**

addition of waist-to-hip ratio to BMI indicated a highly significant effect (p<0·0001), whereas addition of BMI to waist-to-hip ratio had only a modest effect. Similarly, the area under the receiver operator curves of BMI (0·559), waist circumference (0·571), and hip circumference (0·554) were smaller than that of waist-to-hip ratio (0·601). These three methods consistently showed that the waist-to-hip ratio was better than BMI for prediction of myocardial infarction.

Figure 6 shows the relation between a standardised change in the markers and risk of myocardial infarction in various subgroups. The relation between waist-to-hip ratio and risk of myocardial infarction is consistently seen in men and women, old and young individuals, irrespective of the presence of other metabolic risk factors (diabetes, lipid abnormalities), smoking, or hypertension. Thus waist-to-hip ratio is of value in those with high or low levels of other risk factors. A 1 SD increase in waist-to-hip ratio was associated with a significantly greater odds ratio in younger (men <55 years and women <65 years) individuals (1·46, 1·40–1·53) compared with older individuals (1·32, 1·27–1·37, p<0·0001). By contrast, BMI has a variable relation with myocardial infarction in several subgroups, with no association in those with a raised ApoB/Apo-A1 ratio or hypertension. In all subgroups, the odds ratio associated with increased waist-to-hip ratio was larger than with BMI (p<0·0001).

Of the three measures compared, BMI showed the weakest association with myocardial infarction risk in all ethnic groups, with no significant relation in south Asians, Arabs, and mixed-race Africans (table 2). By contrast, waist-to-hip ratio showed a significant association with myocardial infarction in all ethnic groups, and was the strongest marker in six of the eight ethnic groups. Waist circumference was intermediate between waist-to-hip ratio and BMI in its association with myocardial infarction in most ethnic groups apart from Chinese and black Africans, in whom waist circumference was the strongest predictor. Thus, a marker of abdominal obesity was better than BMI as a predictor of myocardial infarction in all ethnic groups.

Table 3 shows the population attributable risk associated with a raised waist-to-hip ratio and raised BMI for the entire sample, for men and women, and for all ethnic groups. Note that use of the waist-to-hip ratio leads to a much larger population-attributable risk than BMI for the association of myocardial infarction with obesity worldwide, and in both sexes. In almost all regions, waist-to-hip ratio was associated with a substantially higher population-attributable risk than a BMI cutoff of over 25 or over 30. Use of the upper two quintiles of the waist-to-hip ratio—ie, a prevalence of 40%—provides ORs of 1·84 (1·75–1·94), and population attributable risk of 24·3% (22·5, 26·2) compared with an OR of 1·22 (1·16–1·29) and population attributable risk of 7·7% (6·0–10·0) for the upper two quintiles of BMI.

Discussion

The INTERHEART study clearly indicates that of the various anthropometric measures commonly used, waist-to-hip ratio shows the strongest relation with the risk of myocardial infarction worldwide. This ratio was the strongest anthropometric predictor of myocardial infarction in men and women, across all age and ethnic groups, in smokers and in non-smokers (potential effect modifier), and in those with or without dyslipidaemia, diabetes, or hypertension (which are consequences of obesity). By contrast, the relation of BMI to myocardial infarction was weaker and less consistent across ethnic and other subgroups. In particular, BMI was not a predictor in those with a history of hypertension or a raised ApoB/ApoA ratio. Moreover, raised waist-to-hip ratio substantially increases the population attributable risk resulting from obesity by over three-fold compared with BMI. Thus the global burden of obesity has been substantially underestimated by the reliance on BMI in previous studies. Also, both waist and hip circumferences are independently related to myocardial infarction, suggesting that both measures are of value for epidemiological and clinical studies. Finally, the association of BMI with myocardial infarction disappears when adjusted for the other risk factors, whereas the associations of waist, hip, and waist-to-hip ratio are still highly significant, suggesting that these latter markers act through mechanisms that differ from other risk factors.

Obesity is an increasing problem worldwide. The prevalence of obesity is generally thought to be highest in developed countries and lowest in Asian countries. However, these conclusions are based on BMI values. If a raised waist-to-hip ratio were to be used to assess the risk of cardiovascular disease, as suggested by the INTERHEART data, the proportion classified as obese worldwide would increase substantially, especially in the middle east, south Asia and southeast Asia.

BMI shows only a modest relation with myocardial infarction overall in our study, and seems to be of no value in several populations, such as Arabs (self-reported ethnicity) or people from southern Asia. By contrast, waist-to-hip ratio indicates the strongest and most consistent relation in most ethnic populations studied. Further, BMI was not predictive of myocardial infarction risk in those with hypertension or raised ApoB/ApoA ratio. By contrast, waist-to-hip ratio suggested consistent associations with myocardial infarction risk in such individuals. These findings imply that the best index of obesity as a predictor of myocardial infarction is the waist-to-hip ratio in most populations.

Waist-to-hip ratio was also better than waist circumference as a measure of risk. This finding could partly relate to adjustment of measures of abdominal circumference for pelvic girth (by measurement of hip), but might also be due to a protective effect associated with larger hip circumferences, since we have noted a significant inverse relation with risk of myocardial infarction (after adjustment for BMI). Previous smaller studies have also reported an inverse relation between increasing hip circumference and diabetes, hypertension, dyslipidaemia, and cardiovascular disease.[20–25] Loss of fat in the hips and limbs during weight reduction is correlated with increases in blood pressure and worsening metabolic risk factors.[24]

Several factors may explain the opposing effects of abdominal and lower-body fat on cardiovascular risk. First, hormonal factors may have different effects on waist, thigh, and hip circumferences, and insulin resistance. For example, glucocorticoid excess, growth hormone deficiency, and high androgen concentrations in women and low testosterone concentrations in men are associated with increased visceral fat, reduced skeletal muscle mass, and insulin resistance.[26] By contrast, endogenous oestrogens stimulate accumulation of subcutaneous gluteal and femoral fat.[27] Second, the opposing effects on cardiovascular risk between abdominal and lower-body fat tissue are probably related to different biochemical characteristics of fat in these regions,[28,29] and differences in secretion of adipokines that contribute to cardiovascular and metabolic risk.[29] Third, increasing hip measurements might also indicate increased gluteal muscle and could be a marker of overall skeletal muscle mass. Indeed, a higher waist-to-hip ratio is known to be associated with decreased muscle mass in the legs and gluteal region.[30] Chowdhury and colleagues[31] showed that higher glucose levels in South Asian men than in Swedish men of the same age and BMI were not due to differences in visceral fat, but were associated with their lower leg muscle mass. Thus, the ratio of fat to muscle (sarcopenic adiposity) can be a measure of risk of cardiovascular disease, which is best estimated by waist-to-hip ratio.

The graded associations seen in our study between both increasing waist and decreasing hip circumferences in relation to myocardial infarction risk, suggest that prevention of cardiovascular disease, diabetes, and other obesity-related conditions need a two-pronged strategy. First, abdominal obesity should be reduced. Second, benefits may also accrue by increasing hip circumference, perhaps by increasing muscle mass or redistribution of fat. At present, very little is known about strategies that specifically reduce abdominal obesity, although overall weight loss probably reduces abdominal obesity. However, if weight loss also leads to a reduction in skeletal muscle mass, this reduction may counteract some of the benefits of weight loss. Therefore, we need to understand the factors affecting abdominal obesity and to increase skeletal muscle mass (or hip size).

Several previous studies have examined the association of BMI, waist-to-hip ratio, or waist circumference, with coronary heart disease.[5–13] The results of these studies have conflicted, with some suggesting that BMI was better than or at least as good as markers of abdominal obesity. Others suggested that markers of abdominal obesity could be better than BMI, but only in younger individuals or only in women. Further, none was able to clearly indicate whether waist circumference or waist-to-hip ratio was the best predictor of myocardial infarction, and the data relating hip size to cardiovascular disease are sparse. Most of these studies had few cardiovascular events (usually less than a few hundred) and so their statistical power to compare different measures was low and the apparent subgroup results reported may well be due to chance.

For reliable assessment of the importance of the various measures overall and in subgroups, studies are needed that include several thousands of events, so that precise estimates can be obtained within each subgroup with each measure. Obtaining such information is possible in INTERHEART, which includes over 12 000 cases of myocardial infarction and several thousand within all subgroups of interest (eg, in old or young individuals). Furthermore, unlike most previous studies, which included mainly individuals of European origin, the inclusion of substantial numbers from all regions of the world makes INTERHEART globally applicable. Finally, we can reliably exclude an increased risk of cardiovascular events at very low BMI (eg, ≤ 20) because we included many such individuals, and showed a graded effect of the waist-to-hip ratio.

An important limitation of our study is that no direct measure of body composition was done. There could be considerable differences in percentage of fat and lean body mass between individuals with similar BMI, especially when this index is compared across different ethnic groups.[32] Waist circumference and waist-to-hip ratio are simple and crude surrogate measures for visceral obesity, which is probably the key determinant of metabolic abnormalities. Therefore, the strong relation between waist-to-hip ratio and myocardial infarction risk in the present study might be an underestimate of the true contribution of visceral fat to cardiovascular disease risk. For example, liposuction of large quantities (>9 kg) of subcutaneous abdominal fat results in large reductions in waist circumference (>12 cm), but has no effect on cardiovascular risk factors.[33] By contrast, surgical removal of even small amounts (<1 kg) of intra-abdominal adipose tissue results in substantial improvements in oral glucose tolerance, insulin sensitivity, and fasting plasma glucose and insulin than in control patients despite similar overall weight loss.[34]

Since our study is mainly focused on myocardial infarction and uses a case-control design, we cannot elucidate the relation between the different measures of obesity on other outcomes (eg, cancers) or whether there is an increased risk of some diseases in those who are very lean. Such an assessment would need very large cohort studies or a meta-analysis of all existing studies. INTERHEART shows that the waist-to-hip ratio is the strongest anthropometric measure that is associated with myocardial infarction risk, and is substantially better than BMI. These results are consistent in both sexes, old and young individuals, in different regions, and in different ethnic groups. Use of raised waist-to-hip ratio as the index of obesity instead of BMI increases the population attributable risk for myocardial infarction threefold. Our findings suggest that substantial reassessment is needed of the importance of obesity for cardiovascular disease in most regions of the world.

Contributors
S Yusuf initiated the INTERHEART study, supervised its conduct and data analysis and had primary responsibility for writing this paper. S Ôunpuu coordinated the worldwide study and reviewed and commented on drafts. S Hawken did all data analyses and reviewed and commented on drafts. S Anand was involved in the design, and along with F Razak and A Sharma, assisted in interpretation and writing the manuscript. All other authors coordinated the study in their respective countries and commented on the manuscript.

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