Body Fat Distribution and Risk of Coronary Heart Disease in Men and Women in the European Prospective Investigation Into Cancer and Nutrition in Norfolk Cohort: A Population-Based Prospective Study

Dexter Canoy, MPhil, MD, PhD; S. Matthijs Boekholdt, MD, PhD; Nicholas Wareham, MBBS, FRCP; Robert Luben, BSc; Ailsa Welch, PhD; Sheila Bingham, PhD; Iain Buchan, MD, FFPH; Nicholas Day, PhD, FRS; Kay-Tee Khaw, MBBChir, FRCP

Background—Body fat distribution has been cross-sectionally associated with atherosclerotic disease risk factors, but the prospective relation with coronary heart disease remains uncertain.

Methods and Results—We examined the prospective relation between fat distribution indices and coronary heart disease among 24,508 men and women 45 to 79 years of age using proportional hazards regression. During a mean 9.1 years of follow-up, 1708 men and 892 women developed coronary heart disease. The risk for developing subsequent coronary heart disease increased continuously across the range of waist-hip ratio. Hazard ratios (95% CI) of the top versus bottom fifth of waist-hip ratio were 1.55 (1.28 to 1.73) in men and 1.91 (1.44 to 2.54) in women after adjustment for body mass index and other coronary heart disease risk factors. Hazard ratios increased with waist circumference, but risk estimates for waist circumference without hip circumference adjustment were lower by 10% to 18%. After adjustment for waist circumference, body mass index, and coronary heart disease risk factors, hazard ratios for 1-SD increase in hip circumference were 0.80 (95% CI, 0.74 to 0.87) in men and 0.80 (95% CI, 0.69 to 0.93) in women. Hazard ratios for body mass index were greatly attenuated when we adjusted for waist-hip ratio or waist circumference and other covariates.

Conclusions—Indices of abdominal obesity were more consistently and strongly predictive of coronary heart disease than body mass index. These simple and inexpensive measurements could be used to assess obesity-related coronary heart disease risk in relatively healthy men and women. (Circulation. 2007;116:2933-2943.)

Key Words: coronary disease □ myocardial infarction □ obesity

Visceral fat accumulation may underlie the adverse metabolic profile associated with obesity.1 Indeed, waist circumference and waist-hip ratio, as indicators of abdominal adiposity,2 have been shown to be better than body mass index, an indicator of total adiposity, for identifying individuals at higher risk of developing atherothrombotic diseases.3 It is plausible that body mass index may be less sensitive than waist circumference or waist-hip ratio at capturing the underlying and disparate metabolic effects of fat depots. A case-control study involving populations worldwide recently reported that waist-hip ratio was associated with acute myocardial infarction independently of, and more strongly than, body mass index.4 However, the prospective relation between fat distribution and coronary heart disease is less clear because findings have been inconsistent.5-20 Many prospective studies reported fewer coronary heart disease events, whereas others relied on self-reported anthropometry. Comparison of risks between sexes is limited because many studies involved only women or men.

Clinical Perspective p 2943

Furthermore, waist and hip circumferences have been shown to have separate and opposite cross-sectional associations with metabolic factors.21-27 The prognostic relevance of these separate associations for future coronary heart disease events is less clear.16,19 We examined the prospective...
relation between indices of fat distribution and future coronary heart disease among men and women in the general population and determined whether this association is independent of body mass index and other conventional coronary heart disease risk factors. We also explored the contribution of hip girth in predicting future coronary heart disease.

Methods

The European Prospective Investigation Into Cancer and Nutrition in Norfolk (EPIC-Norfolk) is a prospective population study of men and women 45 to 79 years of age living in Norfolk, UK, who were recruited from general practice registers during 1993–1997.28 The study was approved by the Norfolk Health District Ethics Committee, and participants signed an informed consent. At the clinic visit, trained research nurses took anthropometric measurements on individuals in light clothing without shoes using a standard protocol.29 Height was measured to the nearest 0.1 cm with a free-standing stadiometer. Weight was measured to the nearest 100 g with digital scales (Salter, UK). We used a D-loop nonstretch fiberglass tape to measure waist circumference (measured at the smallest circumference between the ribs and iliac crest) and hip circumference (measured at the maximum circumference between the iliac crest and the crotch) to the nearest 0.1 cm. We calculated body mass index as weight/height² (kg/m²) and waist-hip ratio as waist circumference/hip circumference. Body mass index was correlated with waist-hip ratio (men = 0.56, women = 0.40) and waist circumference (men and women = 0.85). Both body mass index and waist circumference were correlated with hip circumference in men and women (all coefficients = 0.80). After adjustment for age and sex, the correlations of body mass index with waist, hip, and waist-hip ratio were 0.85, 0.86, and 0.46, respectively, and the correlation of waist to hip was 0.80.

We obtained blood pressure readings and measured serum lipid concentration from nonfasting blood samples.12,22 Participants completed a health and lifestyle questionnaire indicating any family history of heart disease or physician-diagnosed prevalent diseases such as heart attack or myocardial infarction, stroke, and diabetes mellitus. We also assessed cigarette smoking habit (never, former, and current),30 physical activity level (I [sedentary] to IV [most active]),31 and alcohol intake. We further divided current smokers into the categories of 10, 10 to 19, and 20 pack-years of smoking (20 cigarettes per day for 365 days=1 smoking pack-year).

All participants were flagged for death certification at the Office of National Statistics, and vital status was obtained for the whole cohort. Trained nosologists coded all death certificates. Participants admitted to a hospital were identified by their unique National Health Service number, which a local health authority in Norfolk linked to the Hospital Episode Statistics (a database of all hospital contacts throughout the country). We defined coronary heart disease according to the International Classification of Diseases, Ninth Revision codes 410 to 414 or International Statistical Classification of Diseases, Tenth Revision codes I20 to I25. Case ascertainment validation has been described previously.32 A case was considered if a participant had a hospital diagnosis and/or died of coronary heart disease during the follow-up, which ended either on the date of first disease event (diagnosis or death) or on March 31, 2005, for the remaining cohort. We also identified those who only developed fatal or nonfatal acute myocardial infarction (International Classification of Diseases, Ninth Revision code 410 or International Statistical Classification of Diseases, Tenth Revision code I21 to I22).

Statistical Analysis

Of those 25,623 who attended the baseline health check, we analyzed data of 24,508 participants who completed the health and lifestyle questionnaire and had complete anthropometric data. For categorical analyses, we divided participants into sex-specific quintiles of their baseline anthropometry. Using Cox proportional hazards regression, we quantified the risk for developing subsequent coronary heart disease after baseline clinical examination by calculating hazard ratios with and without adjustments for various confounding and mediating biological factors. Different regression models were used because these models could help to assess the usefulness of adiposity indices in predicting coronary heart disease events in general populations (age-adjusted models) as well as for better understanding of disease etiology (multivariable-adjusted models). We chose to take into account factors known to be classic coronary heart disease risk factors that are by themselves modifiable (hypertension, hypercholesterolemia, and smoking) as well as potential confounders because these factors are known to influence adiposity33,34 and independently predict coronary heart disease events.20,35 Our sex-specific multivariable models consisted of the following covariates: age, systolic blood pressure, total cholesterol, cigarette smoking, physical activity, and alcohol intake. We calculated hazard ratios by fifths of adiposity indices (using the bottom fifth as the reference category) and examined risk trends across categories by using adiposity indices as continuous variables (per 1-quintile change) in the regression model. We also calculated hazard ratio for every 1-SD change in adiposity index as well as for every 1-unit change in the adiposity measurement (waist-hip ratio = 0.05, waist circumference = 5 cm, and body mass index = 1 kg/m²) to allow us to compare magnitude of risk estimates, particularly between men and women. To determine the separate associations for waist and hip circumference, we computed the age-adjusted coronary heart disease rates by thirds of waist stratified by hip category (≤102 or >102 cm), which was based on median hip circumference (men = 102 cm, women = 102.3 cm). We standardized disease rates on the basis of the sex-specific age distribution of the whole cohort. We estimated hazard ratios for waist and hip circumference with and without adjustments for each other as well as for body mass index and other covariates.

We also assessed discrimination (the capacity of the model to predict true-positives as opposed to false-positives for a given outcome) by calculating Harrell’s c statistic for the area under the receiver operating characteristic curve of the Cox regression model of age, age², sex, systolic blood pressure, total cholesterol, and cigarette smoking when added to an adiposity parameter (body mass index, waist circumference, waist and hip circumference, or waist-hip ratio). To assess calibration (correspondence between the probability to develop the disease as predicted by a model and the actual disease event), we calculated the estimated risk score for each participant on the basis of the relevant Cox regression model.36 Participants were then categorized into decile of risk scores, and a comparison of the predicted and observed disease event was made for each risk category by calculating the Z score (dividing the difference by the square root of the predicted cases). We also assessed the global goodness of fit of the model by comparing the model with and without the indicator variable for the risk score categories using the likelihood ratio test.37 A better calibration is reflected by a higher probability value, whereas P<0.05 suggests poorer calibration. Furthermore, we assessed the risk estimates for excess adiposity using clinically useful categories of waist-hip ratio (men: <0.95 and ≥0.95; women: <0.80 and ≥0.80) and body mass index (<25, 25 to 29.9, ≥30 kg/m²).38 Age, systolic blood pressure, total cholesterol, and alcohol intake were analyzed as continuous variables, whereas cigarette smoking and physical activity were analyzed as categorical variables in all models. We present disease rates and risk estimates with their 95% CIs and considered P<0.05 significant. We conducted the analyses using Stata 9.2 (StataCorp, College Station, Tex) statistical software.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.
Characteristics | Men (n=11117) | Women (n=13391)  
--- | --- | ---  
Age, y | 60.3 (8.8) | 59.6 (8.8)  
Systolic blood pressure, mm Hg | 137.8 (17.8) | 134.5 (18.9)  
Total cholesterol, mmol/L | 6.05 (1.09) | 6.35 (1.21)  
Body mass index,* kg/m² | 26.6 (3.3) | 26.3 (4.3)  
Waist circumference, cm | 95.9 (9.8) | 82.4 (10.8)  
Hip circumference, cm | 102.8 (6.4) | 103.5 (9.2)  
Waist-hip ratio | 0.932 (0.060) | 0.795 (0.063)  
Alcohol intake, U/wk | 10.1 (11.8) | 4.3 (5.7)  
Current smokers | 12.2 (1341) | 11.2 (1490)  
Former smokers | 55.3 (6101) | 32.5 (4301)  
Never smokers | 32.6 (3598) | 56.3 (7463)  
Sedentary lifestyle† | 29.6 (3299) | 29.4 (3335)  
Prevalent disease‡ | 0.932 (0.060) | 0.795 (0.063)  
Parental history of heart attack | 30.3 (3364) | 32.3 (4332)  

Data are presented as mean (SD) for continuous variables or proportions for categorical variables; proportions may not add up to 100% because of some missing variables.

*Weight/height².
†Physical activity index I.
‡Self-reported physician-diagnosed heart disease, stroke, or diabetes mellitus at baseline.

ratio fifths (P<0.001) but not with higher fifths of waist circumference or body mass index (both P>0.05).

After a mean follow-up of 9.1 years (222,701 person-years), we observed 2600 coronary heart disease events (662 fatal and 1938 nonfatal) with 1708 events in men (27.6% fatal) and 892 events in women (21.4% fatal). When categorized into fifths, an increasing risk for coronary heart disease was observed across the whole range of waist-hip ratio with no apparent threshold in both men and women (Table I in the online-only Data Supplement). The graded linear association was attenuated but persisted after adjustment for various covariates. Figures 1 (men) and 2 (women) show an increasing risk trend with higher waist-hip ratio after adjustment for body mass index and other coronary heart disease risk factors (waist-hip ratio×sex interaction: P>0.05). The association remained significant even when we limited our analysis to nonsmokers and those without prevalent disease. There was no increased risk with higher waist-hip ratio for those with prevalent disease (P for trend>0.05).

Higher waist circumference fifths were associated with higher risks for coronary heart disease, but the strength of the association varied with adjustments for various covariates (Table II in the online-only Data Supplement) and between men and women (waist circumference×sex interaction: P=0.046). In men, a monotonic linear increase was not clearly demonstrated when we adjusted for body mass index and other covariates in men (Figure 1). In women, the linear association persisted despite slight attenuation after adjustment for covariates and exclusion of current smokers and those with prevalent disease (Figure 2). Furthermore, risk estimates for waist circumference in women were almost comparable to the estimates for waist-hip ratio except when analyses were limited to nonsmokers without prevalent disease (Table II in the online-only Data Supplement). There was no increasing risk with higher waist circumference in men and women with prevalent disease (P for trend>0.05).

The age- and covariate-adjusted hazard ratios also increased with increasing fifths of body mass index (Table III in the online-only Data Supplement) in both men and women (body mass index×sex interaction: P>0.05). However, the graded relation was no longer demonstrable with further adjustments for waist-hip ratio and when the analyses were limited to those without prevalent disease and nonsmokers (Figures 1 and 2). Among those with prevalent disease, the linear increase in the hazard ratios with higher body mass index was noted in women (P for trend=0.046) but not in men (P>0.05).

We also explored the role of other lipids as potential biological mediating factors. With adjustment for covariates as well as high-density lipoprotein cholesterol, nonfasting triglycerides, and body mass index, the linear increase in risk across waist-hip ratio fifths was attenuated but remained significant in men (P for trend <0.001) and women (P for trend=0.003) even after exclusion of those with prevalent disease (P for trend: men, P<0.001; women, P=0.023); the increasing risks across waist circumference categories was observed for all women (P for trend=0.035), including women without prevalent disease (P for trend=0.041), but not in men (P for trend >0.05). Across fifths of body mass index, increasing risks were observed in men (P for trend=0.007) and weakly for women (P for trend=0.097). We did not observe significant trends among those without prevalent disease or after substituting waist-hip ratio for waist circumference in the multivariable models (all P for trend >0.05).

When the risk was assessed in various subgroups, as shown in Table 2, we found increased risks for higher waist-hip ratio in all subgroups except in men with parental history of myocardial infarction or who had early coronary heart disease (occurring within 5 years of follow-up) and among men and women with prevalent disease. Statistical interactions were significant in men for waist-hip ratio with prevalent disease (P=0.040), family history of myocardial infarction (P=0.002), and early coronary heart disease events (P=0.001) and in women for waist-hip ratio with early coronary heart disease events (P=0.001). Waist circumference was also associated with increased risk among women for all subgroups except for those with prevalent disease (P for interaction=0.020). However, the risk estimates for waist circumference in men were smaller in magnitude and had wider CIs.

When separate associations for waist and hip circumference were assessed, higher waist circumference was associated with higher age-adjusted coronary heart disease rates, but at any given waist circumference, those with bigger hips
had lower disease rates than those with smaller hips (Figure 3). Table 3 shows the risk estimates for waist and hip circumference; their simultaneous adjustment showed that these indices were related to coronary heart disease, even after adjustment for each other, and in opposite directions, ie, increasing risk with bigger waist circumference but decreasing risk with bigger hip circumference (model 3). Findings were consistent even when we excluded those with prevalent disease. With the use of a similar covariate-adjusted model, Figure 4 shows the hazard ratio by waist and hip circumference quintiles with simultaneous adjustment for each other as well as for body mass index and other risk factors. When those with prevalent disease were excluded, the opposite trends remained significant for waist and hip girth in men (P<0.001) and waist girth in women (P=0.001) but weakly for hip girth (P=0.099).

When acute myocardial infarction occurring after baseline recruitment was used as the end point (855 events), the body mass index– and covariate-adjusted hazard ratios per 0.05 increase in waist-hip ratio were 1.13 (95% CI, 1.05 to 1.23) in men and 1.25 (95% CI, 1.13 to 1.39) in women, and per 5-cm increase in waist circumference the risks were 1.10 (95% CI, 1.02 to 1.19) in men and 1.24 (95% CI, 1.12 to 1.38) in women. Exclusion of those with prevalent disease showed comparable risk estimates. The covariate-adjusted hazard ratios per 1-kg/m² increase in body mass index were 1.03 (95% CI, 1.01 to 1.06) in men and 1.05 (95% CI, 1.02 to 1.08) in women. These risk estimates were attenuated in both men and women when waist-hip ratio or waist circumference was added to the model and when we excluded those with prevalent disease heart disease, stroke, or diabetes (both P>0.05).

We assessed how adiposity measures improved the prediction of coronary heart disease among those without prevalent disease. The area under the receiver operating characteristic curve increased modestly when an adiposity term was added to the baseline model of age, sex, and standard coronary heart disease risk factors (Table 4). The probability values were <0.05 for all models, suggesting poor overall goodness of fit for the models. However, when the calibration in each stratum of risk was examined, divergence of the observed from the predicted number of disease events was observed mainly in the lowest 2 risk strata for most models, with the risk models predicting up to twice the number of observed disease events. When we limited our analyses to noncurrent smokers, calibration for the models improved, particularly for models with terms for waist and hip or waist-hip ratio (Table IV in the online-only Data Supplement). Finally, when we estimated risks by clinical cut points for body mass index and waist-hip ratio, highest risks were associated with higher body mass index and waist-hip ratio (Table V in the online-only Data Supplement). Even among lean individuals (body mass index <25 kg/m²), those with higher waist-hip ratio had ≤50% higher risk than those with lower waist-hip ratio. These risks were not explained by conventional risk factors.

Discussion
We observed a continuous and graded relation between waist-hip ratio and subsequent coronary heart disease event,
particularly among men and women who were relatively healthy at baseline recruitment. The association persisted even after body mass index and conventional coronary heart disease risk factors were taken into account and could reflect the separate and opposite associations of waist and hip circumference with coronary heart disease. Waist-hip ratio, waist circumference, and body mass index were directly related to development of coronary heart disease, but the magnitude and shape of the associations were influenced by adjustments for possible mediating biological factors and potential confounders. Describing the nature of the association between adiposity and coronary heart disease with the use of different models could be useful for different purposes, such as in assessing coronary heart disease risk in the general population (age-adjusted models) and understanding the biological pathways underlying the observed associations (multivariable models). However, regardless of the model used, waist-hip ratio was independently and more consistently predictive of coronary heart disease than waist circumference or body mass index in both men and women.

Body mass index remained predictive of coronary heart disease, but risk estimates were greatly attenuated when fat distribution, biological mediating factors, and prevalent disease were considered. Because it is simple to use, waist circumference alone may be used because it has been shown to be cross-sectionally associated with coronary heart disease risk factors5 and may predict future disease events.12,14,18 In our cohort, waist circumference predicted future coronary heart disease events, but the magnitude of its effect was lower than that of waist-hip ratio, particularly in men. The effect modification by hip circumference suggests that coronary heart disease risk may be underestimated when waist circumference alone is used. Because waist circumference is highly correlated with hip circumference and body mass index, the adverse metabolic effect of abdominal fat deposition may not be captured when waist circumference is used without the separate effects of body mass index or hip girth being taken into account. Similarly, the risks associated when hip circumference alone is used may reflect the effect of total adiposity; lower risks associated with higher hip girth may not be observed without total body size being taken into account. Indeed, other studies have similarly observed that the inverse association between hip circumference and disease event was contingent on adjustment for total body size such as body mass index.4,16 On the other hand, waist-hip ratio could be a simple but more consistent indicator of the combined risk estimates for central and peripheral adiposity in both men and women.

A number of studies addressed the prospective relation of waist circumference or waist-hip ratio with coronary heart disease with body mass index taken into account, but results have been inconsistent.5–20 Associations for abdominal adiposity independent of body mass index and other covariates were shown in some studies5,9,11,17 but not in others.5,15,16 Others report an independent association for waist-hip ratio only in men,9 women,6,12,14 or older participants.10 The prediction for coronary heart disease could also differ be-
Table 2. Risk for Coronary Heart Disease per 1-Unit Change in Fat Distribution Measure, Stratified by Covariates, in Men and Women 45 to 79 Years of Age

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men (n=11 117)</th>
<th></th>
<th>Women (n=13 391)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-Years</td>
<td>Cases (n)</td>
<td>WHR (per 0.05)</td>
<td>Waist (per 5 cm)</td>
</tr>
<tr>
<td>Body mass index*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>331 880</td>
<td>452</td>
<td>1.12 (1.02 to 1.23)</td>
<td>1.04 (0.96 to 1.13)</td>
</tr>
<tr>
<td>≥25 kg/m²</td>
<td>66 606</td>
<td>1256</td>
<td>1.11 (1.06 to 1.17)</td>
<td>1.08 (1.04 to 1.11)</td>
</tr>
<tr>
<td>Current smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>87 053</td>
<td>1481</td>
<td>1.08 (1.03 to 1.14)</td>
<td>1.02 (0.97 to 1.08)</td>
</tr>
<tr>
<td>Yes</td>
<td>11 742</td>
<td>227</td>
<td>1.11 (0.97 to 1.27)</td>
<td>1.05 (0.92 to 1.20)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>66 124</td>
<td>743</td>
<td>1.13 (1.07 to 1.20)</td>
<td>1.10 (1.03 to 1.17)</td>
</tr>
<tr>
<td>≥65 y</td>
<td>33 670</td>
<td>965</td>
<td>1.06 (1.00 to 1.13)</td>
<td>0.99 (0.93 to 1.06)</td>
</tr>
<tr>
<td>Prevalent disease†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>91 105</td>
<td>1183</td>
<td>1.12 (1.05 to 1.19)</td>
<td>1.05 (0.99 to 1.12)</td>
</tr>
<tr>
<td>Yes</td>
<td>7689</td>
<td>525</td>
<td>1.01 (0.93 to 1.09)</td>
<td>0.95 (0.87 to 1.03)</td>
</tr>
<tr>
<td>Parental history of heart attack</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>69 454</td>
<td>1125</td>
<td>1.14 (1.07 to 1.21)</td>
<td>1.05 (0.99 to 1.11)</td>
</tr>
<tr>
<td>Yes</td>
<td>29 235</td>
<td>581</td>
<td>1.01 (0.94 to 1.09)</td>
<td>0.97 (0.89 to 1.05)</td>
</tr>
<tr>
<td>Early CHD cases‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>96 726</td>
<td>1005</td>
<td>1.11 (1.04 to 1.18)</td>
<td>1.02 (0.96 to 1.09)</td>
</tr>
<tr>
<td>Yes</td>
<td>2068</td>
<td>702</td>
<td>0.96 (0.89 to 1.04)</td>
<td>0.96 (0.89 to 1.03)</td>
</tr>
</tbody>
</table>

WHR indicates waist-hip ratio; CHD, coronary heart disease. All values were adjusted for all listed variables (but not early CHD cases) and for systolic blood pressure, total cholesterol, physical activity, and alcohol intake except when used for stratification. In men, all P for interaction between fat distribution measure and covariate >0.10 except for WHR and prevalent disease (P=0.036), WHR and parental history of heart attack (P=0.002), WHR and early CHD cases (P=0.001), waist circumference and age (P=0.051), waist circumference and prevalent disease (P=0.060), and waist circumference and early CHD cases (P=0.001). In women, all P for interaction between fat distribution measure and covariate >0.10 except for WHR and early CHD cases (P<0.001), waist circumference and being overweight (P=0.069), waist circumference and cigarette smoking (P=0.009), and waist circumference and early CHD cases (P=0.009).

*Weight/height².
†Physician-diagnosed heart disease, stroke, or diabetes mellitus at baseline. ¶CHD occurring within 5 years of follow-up.

WHR was related to a risk reduction of up to 44% in men and 33% in women after waist circumference, body mass index, and other conventional risk factors were taken into account. Moreover, adjustment for hip circumference increased the risk prediction afforded by using waist circumference alone by ≈10% to ≈18% in men and women (risk difference between models 3 and 1, Table 2).

Our results are comparable to the findings in INTERHEART, a case-control study involving populations across 52 countries that reported waist-hip ratio to be more strongly associated with acute myocardial infarction than body mass index. They estimated an increased risk of 37% per 0.085 change in waist-hip ratio (after adjustment for age, sex, region, and body mass index), which is close to our estimate of 39% increase in risk (based on a comparable regression model with acute myocardial infarction used as the disease outcome). Each 12.08-cm change in waist circumference and 10.96-cm change in hip circumference in their study was associated with reduced type 2 diabetes incidence, aortic calcification progression in women, and coronary heart disease events in women but not in men. In our cohort, the top hip circumference fifth was related to a risk reduction of up to 44% in men and 33% in women after waist circumference, body mass index, and other conventional risk factors were taken into account. Moreover, adjustment for hip circumference increased the risk prediction afforded by using waist circumference alone by ≈10% to ≈18% in men and women (risk difference between models 3 and 1, Table 2).
associated with a 25% increase and 13% decrease in risk, respectively, after adjustment for age, sex, region, and body mass index. Using a comparable model, we report a 66% increased risk for waist circumference and 21% reduced risk for hip circumference. Our results also show a significant 9% increased risk for every 4.15-kg/m² change in body mass index after adjustment for age, sex, and waist-hip ratio compared with only 2% in INTERHEART. The magnitude of the association for each anthropometry differed slightly, perhaps reflecting variation in body fat and lean mass according to ethnicity or medical condition during recruitment. Unlike participants in INTERHEART, our cohort involved mainly white subjects who were not recruited on the basis of disease status. Nevertheless, the consistency in the results for waist-hip ratio for men and women in both studies suggests that it could be a useful measure for assessing obesity-related risk for atherosclerotic disease within and between populations.

Variation in risks by the anatomic location of fat could reflect differences in metabolic characteristics between abdominal and peripheral body fat. Increased abdominal obesity could indicate increased visceral fat accumulation, which is associated with elevated lipolysis and portal fatty acid efflux, thereby promoting an atherogenic lipid profile, decreasing hepatic clearance of insulin, and increasing peripheral hyperinsulinemia. Regional variations in adipokine secretions have also been observed. Because the adverse metabolic profile of obese individuals improved with omentectomy but not with abdominal subcutaneous fat liposuction, the subcutaneous portion of the abdominal fat is unlikely to contribute to disease risk. On the contrary, subcutaneous fat, which comprises 85% of total body fat, may help to regulate metabolism by buffering the elevated postprandial fatty acid and lipid fluxes. Peripheral body fat, which is mainly stored subcutaneously in femoral, gluteal, and thigh regions, has lower lipolytic activity than abdominal body fat. It is plausible that peripheral adipose tissue serves as a "metabolic sink" by taking up excess circulating fatty acids and even preventing ectopic fat accumulation, a morphological feature of insulin resistance. Indeed, absence of subcutaneous fat such as in lipodystrophy is associated with insulin resistance, dyslipidemia, and fatty liver. In animals, improvements in insulin sensitivity and lipid profile have been observed in transgenic lipoatrophic mice after transplantation of adipose tissue subcutaneously. In humans, relatively greater peripheral adiposity has been associated with lower blood pressure, healthier lipid profile, and better glucose homeostasis and insulin sensitivity. The associations for waist-hip ratio that we observed could reflect the separate and opposite metabolic effects of central and peripheral adiposity, as indicated by waist and hip circumference, respectively.

Sex hormones, growth hormones, corticosteroids, and genetic factors contribute to fat patterning. However, little is known about modifiable factors that influence fat distribution. Studies suggest that not smoking, physical activity, and a healthy diet could contribute to healthier fat distribution.
an ideal adiposity phenotype is unlikely to be feasible, although a randomized controlled trial suggested that exercise led to reduction in fat mass, including waist and hip girths.34 Because waist and hip girths are highly correlated, those with bigger hips are likely to have bigger waist circumference and should therefore benefit from reducing excess fat. Our findings suggested that reducing weight by 1 kg (for a given height) could translate to reducing coronary heart disease risk by 2% in both men and women. Alternatively, reducing waist circumference

Table 3. Risk for Coronary Heart Disease per 1-SD Increase in Waist and Hip Circumference in Men and Women 45 to 79 Years of Age

<table>
<thead>
<tr>
<th>Regression Model* (1 SD)</th>
<th>All</th>
<th>Age-Adjusted</th>
<th>Covariate-Adjusted†‡</th>
<th>Without Prevalent Disease (Covariate-Adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1: Waist circumference (9.8 cm)</td>
<td>n=11 117 (1708 cases, 98 794 person-years)</td>
<td>1.23 (1.18 to 1.29)</td>
<td>1.20 (1.14 to 1.26)</td>
<td>1.18 (1.11 to 1.25)</td>
</tr>
<tr>
<td>Model 2: Hip circumference (6.4 cm)</td>
<td>1.10 (1.05 to 1.15)</td>
<td>1.09 (1.31 to 1.14)</td>
<td>1.08 (1.02 to 1.14)</td>
<td></td>
</tr>
<tr>
<td>Model 3: Waist circumference (9.8 cm)</td>
<td>1.40 (1.30 to 1.50)</td>
<td>1.34 (1.24 to 1.45)</td>
<td>1.32 (1.19 to 1.45)</td>
<td></td>
</tr>
<tr>
<td>Hip circumference (6.4 cm)</td>
<td>0.85 (0.79 to 0.92)</td>
<td>0.90 (0.83 to 0.97)</td>
<td>0.87 (0.79 to 0.96)</td>
<td></td>
</tr>
<tr>
<td>Model 4: Waist circumference (9.8 cm)</td>
<td>1.21 (1.10 to 1.33)</td>
<td>1.17 (1.06 to 1.29)</td>
<td>1.20 (1.06 to 1.35)</td>
<td></td>
</tr>
<tr>
<td>Hip circumference (6.4 cm)</td>
<td>0.78 (0.72 to 0.84)</td>
<td>0.80 (0.74 to 0.87)</td>
<td>0.83 (0.75 to 0.92)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (3.3 kg/m²)</td>
<td>1.29 (1.18 to 1.42)</td>
<td>1.27 (1.15 to 1.40)</td>
<td>1.17 (1.04 to 1.07)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1: Waist circumference (10.8 cm)</td>
<td>n=13 391 (892 cases, 907 person-years)</td>
<td>1.35 (1.27 to 1.44)</td>
<td>1.29 (1.20 to 1.38)</td>
<td>1.26 (1.17 to 1.36)</td>
</tr>
<tr>
<td>Model 2: Hip circumference (9.2 cm)</td>
<td>1.20 (1.12 to 1.27)</td>
<td>1.16 (1.08 to 1.24)</td>
<td>1.14 (1.05 to 1.22)</td>
<td></td>
</tr>
<tr>
<td>Model 3: Waist circumference (10.8 cm)</td>
<td>1.55 (1.39 to 1.72)</td>
<td>1.45 (1.30 to 1.63)</td>
<td>1.42 (1.25 to 1.62)</td>
<td></td>
</tr>
<tr>
<td>Hip circumference (9.2 cm)</td>
<td>0.85 (0.77 to 0.94)</td>
<td>0.90 (0.80 to 1.00)</td>
<td>0.86 (0.76 to 0.98)</td>
<td></td>
</tr>
<tr>
<td>Model 4: Waist circumference (10.8 cm)</td>
<td>1.41 (1.25 to 1.59)</td>
<td>1.38 (1.21 to 1.57)</td>
<td>1.38 (1.19 to 1.59)</td>
<td></td>
</tr>
<tr>
<td>Hip circumference (9.2 cm)</td>
<td>0.74 (0.64 to 0.85)</td>
<td>0.80 (0.69 to 0.93)</td>
<td>0.82 (0.69 to 0.97)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (4.3 kg/m²)</td>
<td>1.27 (1.18 to 1.48)</td>
<td>1.14 (0.96 to 1.34)</td>
<td>1.09 (0.91 to 1.31)</td>
<td></td>
</tr>
</tbody>
</table>

Values are hazard ratio (95% CI). Prevalent disease refers to reported physician-diagnosed heart disease, stroke, or diabetes mellitus at baseline.

*Waist and hip circumference used separately (models 1 and 2), together (model 3), or with additional adjustment for body mass index (model 4) in the Cox regression model.
†Covariates were age, systolic blood pressure, total cholesterol, cigarette smoking, physical activity, and alcohol intake.
‡Because of missing values, numbers were lower in covariate-adjusted models for all (10 364 men [1583 cases] and 12 230 women [798 cases]) and for those without prevalent disease (10 364 men [1583 cases] and 12 230 women [798 cases]).

Figure 4. Hazard ratios for coronary heart disease by waist and hip circumference quintiles in men and women 45 to 79 years of age. Estimates were obtained by simultaneously adding the categorical terms for waist and hip circumference quintiles in a sex-specific Cox regression model with adjustment for body mass index, age, systolic blood pressure, total cholesterol, cigarette smoking, physical activity, and alcohol intake.
by 5 cm could lower risk by 11% in men and 15% in women. Such magnitudes of reduction in weight or waist circumference are achievable with dietary restriction and low-intensity walking 3 times per week.34,53

We used only surrogate indicators of body composition and could not delineate separate associations for different fat depots. More accurate measures of fat distribution may be needed to improve risk assessment in specific subgroups in the population. Further studies are needed to assess to what extent central adiposity measurement can improve disease prediction with the use of existing coronary heart disease risk models. Reduced hip circumference could reflect muscle atrophy observed in insulin resistance or diabetes,54 which is related to increased risk for coronary heart disease.55 Although we accounted for prevalent illness in our analyses, we did not assess insulin sensitivity directly. However, we used a prospective study design, showed data for both men and women, and had sufficient power to examine in more detail the nature of the association between adiposity and coronary heart disease, particularly the separate associations for waist and hip girths.

The population-attributable risk estimates based on body mass index might be grossly underestimated up to 3-fold.4 Because our results suggested that waist-hip ratio was more consistently associated with coronary heart disease than body mass index in both men and women, this simple and inexpensive measure could be useful not only for improving coronary heart disease risk assessment but also for estimating the burden of obesity-related coronary heart disease in the general population. Peripheral adiposity, which is often neglected when the health risks of excess fat are studied, should be taken into account for better prediction of coronary heart disease by waist circumference. Nevertheless, regardless of how adiposity is distributed, the challenge remains the same: to reduce the prevalence of obesity and prevent weight gain due to excess fat in the general population.

Acknowledgments
The authors extend their appreciation to EPIC-Norfolk Study participants, staff members, and collaborating general practices and hospitals.

Sources of Funding
The EPIC-Norfolk Study is supported by program grants from Cancer Research UK and the Medical Research Council with additional grants from the Stroke Association, British Heart Foundation, Department of Health, Europe Against Cancer Programme Commission of the European Union, Food Standards Agency, and Wellcome Trust. Dr Canoy was supported by Cambridge Commonwealth Trust/Cambridge Overseas Trust and Christ’s College.
None.

References


**CLINICAL PERSPECTIVE**

The obesity-associated increased risk for developing coronary heart disease (CHD) could be due to the adverse metabolic profile associated with increased visceral fat accumulation rather than to subcutaneous fat, which comprises >85% of total body fat. However, using more sophisticated instruments, such as magnetic resonance imaging, to accurately quantify fat in specific depots is impractical for use in a clinical setting. Simple anthropometric measures, which are known to correlate with fat distribution, would therefore be preferred. Body mass index, which is weight/height$^2$, is a measure used to define overweight and obesity, but this measure does not provide enough information on fat distribution. Alternatively, waist circumference could be measured and is simple enough for use in assessing abdominal obesity over time. However, waist girth is correlated with hip circumference, a measure that showed an independent and seemingly “protective” effect on CHD. Without hip girth being taken into account, the use of waist circumference alone may underestimate true CHD risk. Waist-hip ratio could be an alternative measure to use because it is strongly predictive of CHD in both men and women. Even among lean individuals (body mass index <25 kg/m$^2$), an increased waist-hip ratio was associated with higher CHD risk, suggesting that the impact of excess visceral fat can be observed even without gaining so much weight as to be considered overweight or obese. However, despite the need to reduce excess weight in healthy individuals, the role of excess weight reduction in patients with known history of cardiovascular disease or diabetes needs further investigation.
Body Fat Distribution and Risk of Coronary Heart Disease in Men and Women in the European Prospective Investigation Into Cancer and Nutrition in Norfolk Cohort: A Population-Based Prospective Study
Dexter Canoy, S. Matthijs Boekholdt, Nicholas Wareham, Robert Luben, Ailsa Welch, Sheila Bingham, Iain Buchan, Nicholas Day and Kay-Tee Khaw

_Circulation_. 2007;116:2933-2943; originally published online December 10, 2007; doi: 10.1161/CIRCULATIONAHA.106.673756

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/116/25/2933

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2008/01/10/CIRCULATIONAHA.106.673756.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/