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ABSTRACT

Background: Excessive body weight is known to cluster with cardiovascular (CV) risk factors, but it is not clear which anthropometric obesity measure provides best independent predictive value of coronary artery disease (CAD).

Methods and results: We explored associations between CAD and four different obesity measures (body mass index (BMI), waist circumference, waist/height and waist/height²) in a cohort of 16,657 subjects (40.4% men; 20.8% CAD patients), recruited by 700 primary care physicians in 444 Polish cities. 42.8% of subjects were classified as overweight, 31.7% as obese and 39.8% had abdominal obesity. In univariate analyses all obesity measures correlated with CAD (p < 0.001), but waist/height² was the strongest discriminator between CAD patients and controls. Age-adjusted and sex-adjusted analyses confirmed a graded increase in CAD risk across distributions of all four obesity measures—1 standard deviation (SD) increase in BMI, waist circumference, waist/height and waist/height² increased the odds of CAD by 1.23, 1.24, 1.26 and 1.27, respectively (all p < 0.001). In models fully adjusted for CV risk factors, waist/height² remained the strongest obesity correlate of CAD, being the only independent associate of CAD in men. In a fully adjusted BMI—waist circumference stratified model, sarcopenic obesity (waist > median, BMI < median) and simple obesity (waist and BMI > median) were the strongest independent associates of CAD in men (p = 0.008) and women (p < 0.001), respectively.

Conclusion: This cross-sectional study showed that waist/height² may potentially offer a slightly higher predictive value of CAD than BMI or waist circumference and revealed an apparent sexual dimorphism in correlations between obesity measures and CAD.

Obesity has been widely recognised as a major risk factor for coronary artery disease (CAD) and myocardial infarction,1,2 progression from stable CAD to myocardial infarction (MI)3 and cardiovascular mortality.4 These apparent associations between obesity and coronary atherosclerosis have their roots early in life, before any clinical manifestations of heart disease.5 The majority of these correlations were documented based on the most commonly used estimate of adiposity—body mass index (BMI). However, accumulating evidence suggests that the distribution of the body fat impacts on cardiovascular risk and that abdominal adiposity (measured by waist circumference) may be a stronger cardiovascular risk factor than BMI.6–8 Other anthropometric indices such as waist/hip ratio, waist/height ratio (WHtR, WSR = waist/height²) and waist/height² ratio have been proposed as clinically reliable surrogates of cardiovascular risk. Waist/hip ratio was shown to correlate best with myocardial infarction in a large multi-ethnic study,9 while waist/height ratio was implicated as the most accurate obesity-related discriminator of cardiovascular risk in a large prospective study and a meta-analysis.10 Given that height² is used to calculate BMI, waist circumference indexed to height² could be considered as a potentially more accurate obesity-related associate of cardiovascular risk. However, large studies are missing for this anthropometric measure.11 Current guidelines recommend the assessment of both BMI and waist circumference.12 The combination of BMI and waist circumference has gained further relevance as the coincidence of low BMI with high waist circumference (“sarcopenic obesity”) was reported to predict a poor cardiovascular outcome.13 The paucity of data on relations between CAD and obesity measures is particularly striking in relation to populations of Eastern Europe, despite accumulating evidence for a significant impact of the recent social and economic transformation on the prevalence of cardiovascular risk factors in this region.14 To address these issues we have analysed crude and adjusted associations between CAD and four different obesity measures (BMI, waist circumference, waist/height and waist/height²) in a large sample of subjects recruited through a national screening in Poland.

METHODS

Subjects

Subjects of the Lipidogram 2004 study were recruited in October–December 2004 by 700 primary care physicians in 444 cities across Poland. The distribution of study sites (and hence the number of patients recruited) was defined in proportion to the populations of the 16 regions of Poland (supplementary figure 1, supplementary table 1 on Heart website). All participating physicians received a special training regarding the study protocol, procedures and the standar-
dised questionnaire. Patients were eligible if they were aged ≥30 years, presented to their primary care doctors with any medical problem during the study recruitment and gave their written consent to participate in the baseline evaluation (2004) and follow-up surveys. Exclusion criteria were dementia or other mental condition resulting in inability to give informed consent, and incomplete clinical or biochemical information. Subjects were also excluded if they were planning to move house as they would be lost for follow-up observations (a 4–5-year follow-up observation of at least 10% subjects recruited in 2004). The diagnosis of history of CAD and MI was confirmed by the participating physicians based on medical information available in clinical documentation. The presence of diabetes mellitus, hypertension and dyslipidaemia was diagnosed by the physicians based on history and medical records. History of hyperlipidaemia is a personal history of documented elevation of total cholesterol (>5.2 mmol/l) or low-density lipoprotein (LDL)-cholesterol (>4.1 mmol/l) or of lipid-lowering medication before recruitment into the study. In addition, all subjects with plasma cholesterol levels >5.2 mmol/l and/or LDL-cholesterol >4.1 mmol/l in biochemical analysis conducted in the central laboratory after recruitment were also classified as hyperlipidaemic. Diabetes was defined as a record of diabetes, of increased fasting glucose (>7 mmol/l), of increased random plasma glucose (>11.1 mmol/l) or of use of antidiabetic drugs or insulin. Hypertension was defined as record of elevated systolic blood pressure (BP) (>140 mm Hg) and/or diastolic BP (>90 mm Hg) and/or antihypertensive drugs or a medical record of hypertension. Smoking was defined as current smoking of ≥1 cigarette/day. Anthropometric measurements were carried out on the day of blood collection. Weight and height were measured without heavy clothing and shoes; waist circumference was measured over the unclothed abdomen at a level of the midpoint between the lower margin of the ribs and the anterior superior iliac crest spine. A blood sample was taken from patients fasting for ≥12 hours. Lipid analyses were performed from serum samples in a central laboratory within 12 hours after drawing; transport was organised in cooled containers. Total cholesterol, high-density lipoprotein (HDL)-cholesterol (HDL-C) and triglycerides were determined by standard colorimetric-enzymatic methods, LDL-cholesterol (LDL-C) was calculated using the Friedewald formula. All patients gave written, informed consent. The study was approved by the bioethical committee of the Polish Chamber of Physicians and conforms to the principles outlined in the Declaration of Helsinki.

Statistical analyses

A total of 17 065 subjects were recruited in this survey; 289 patients were excluded for inconsistent or implausible data; 119 for insufficient data (missing waist circumference); leaving 16 657 individuals eligible for the current analyses. Continuous variables were summarised by means (SD) and were analysed using t tests or non-parametric tests, depending on their distribution. The crude association of obesity measures with CAD was assessed using receiver operating curves (ROC). Confidence intervals and p values (for rejecting the null hypothesis of area under the curve (AUC) = 0.5) were calculated assuming a non-parametric distribution. Adjusted associations of obesity measures with CAD were explored using logistic regression models. We used two specific models, (1) adjusted only for age and gender (where applicable), and (2) adjusted for multiple cardiovascular risk factors. The latter multivariate analyses were based on conditional backward regression including age, gender (where applicable), hypertension, hyperlipidaemia, HDL-C and diabetes as potential confounders. In conditional backward regression, all covariates are forced in the model in the first step; then covariates under a certain probability threshold (exclusion threshold) are excluded stepwise. In each step, all excluded covariates are re-evaluated and if they reach a certain probability threshold (inclusion threshold), they are re-included into the model. In our analyses, exclusion probability threshold was set to p = 0.1, inclusion threshold to p < 0.05. Conditional backward regression is superior to forward regression because it does not miss significant covariates due to suppressor effects (that is, a variable is only significant if the model is corrected for another variable).

For all regression analyses obesity measures were z-score transformed so that the respective β-coefficients were calculated for 1 SD. In gender specific models z-score transformations were performed in each gender separately.

All analyses were carried out using SPSS Version 16.

RESULTS

General clinical characteristics and estimates of obesity prevalence

The details of demographic and clinical characteristics of the study group are given in table 1 and supplementary table 2. In all, 42.8% (7130) of subjects in this survey were classified as overweight (BMI >25 kg/m² and <30 kg/m²) and 31.7% (5287) as obese (BMI >30 kg/m²); 39.8% (6624) satisfied the criteria of abdominal obesity (defined by waist circumference >102 cm in men and >88 cm in women). Both overweight and obesity were more prevalent in men than in women (48.0% (3235) vs 39.2% (63897), p < 0.001, and 32.9% (2211) vs 31.0% (3076), p = 0.01, respectively; supplementary table 2). Obesity was more prevalent in patients with CAD than in controls (50.1% (1558) vs 29.8% (3954), p < 0.001), while overweight prevalence was not significantly different in patients and controls (45.5% (1508) vs 42.6% (5622), p = 0.52). Abdominal obesity was significantly more common in patients with CAD than in controls (50.2% (1738) vs 37.8% (4868), p < 0.001) and much less prevalent in men compared to women (27.7% (1864) vs 47.9% (4760), p < 0.001; supplementary table 2).

Anthropometric obesity measures and CAD

In crude analyses based on ROC, all four assessed obesity measures (BMI, waist, waist/height, waist/height²) proved to have highly significant potential to discriminate between subjects with CAD and controls. In the entire cohort and both genders analysed separately, waist/height² showed the highest area under the ROC (AUC in entire cohort 0.620 (95% CI 0.610 to 0.630), in men 0.611 (0.595 to 0.626), in women 0.638 (0.625 to 0.651), all p < 0.001, supplementary table 3).

In regression models adjusting for age and gender, waist/height² was confirmed as the strongest correlate of coronary artery disease (table 2, fig 1). Specifically, subjects from the third tertile of waist/height² distribution had a 1.89-increased odds ratio (OR) for CAD compared to the first tertile. For BMI, waist circumference and waist/height, the corresponding ORs were 1.63, 1.62 and 1.81, respectively (table 2). The separate analysis of men and women showed that waist/height² was the most superior correlate of age-adjusted risk of CAD in both genders. Generally, all four obesity measures were better correlates of CAD in women than in men. However, women exhibited only modest differences between the four measures. In the categorised tertile model in females, waist/height showed even
slightly stronger OR of CAD than waist/height\textsuperscript{2} (2.12 (1.84 to 2.44) vs 1.99 (1.73 to 2.29); table 2).

To assess associations between CAD and the obesity measures in the context of other cardiovascular risk factors, we performed fully adjusted analyses including diabetes, hyperlipidaemia, hypertension and HDL-C as covariates. In conditional backward regression models waist/height \textsuperscript{2} was the strongest correlate of CAD in the entire cohort (OR for 1 SD increase 1.12 (1.08 to 1.17), \( p = 0.001 \); table 3). Multivariate adjusted models performed separately in men and women revealed consistent results—in both genders, waist/height \textsuperscript{2} showed the strongest association with CAD (OR for 1 SD increase 1.12 (1.08 to 1.17), \( p = 0.001 \); table 3). In men waist/height \textsuperscript{2} was the only obesity measure that remained significant in the fully adjusted model.

Combination of anthropometric obesity measures and CAD (waist circumference—BMI stratified analysis)

To explore the impact of a combination of two most commonly used anthropometric obesity measures (BMI and waist circumference) on CAD, we divided our cohort into for four gender-specific groups: (1) BMI > median, waist circumference > median (“simple obesity”), (2) BMI < median, waist > median (“sarcopenic obesity”), (3) BMI > median, waist < median (“high fat-free mass”) and (4) BMI < median, waist < median (control group).

In men, both the “simple obesity” group and the “sarcopenic obesity” group had a significantly increased odds of CAD in an age-adjusted model (OR 1.55 (95% CI 1.30 to 1.85), and 1.45 (1.19 to 1.76), respectively, both \( p < 0.001 \), supplementary table 4). However, in the model fully adjusted for available cardiovascular risk factors, only the “sarcopenic obesity” group showed an increased risk of CAD compared to the control group (OR 1.31 (1.07 to 1.60), \( p = 0.008 \)). In contrast, in women the “simple obesity” group had the highest risk of CAD in both the age-adjusted and the fully adjusted model (OR 1.79 (1.58 to 2.03), and 1.53 (1.16 to 1.52), respectively, both \( p < 0.001 \), supplementary table 4).

DISCUSSION

In the present study we have analysed associations between CAD and different anthropometric measures of obesity in a
large sample representative of the current middle-aged population of Poland. Our data suggest that there is an epidemic of excessive body weight in middle-aged and elderly Eastern European subjects, in particular among patients with CAD. The higher prevalence of obesity and overweight in our cohort than in a recent epidemiological meta-analysis \(^1\) reflects most likely the significant differences in age range between subjects recruited into our study (>30 years) and studies investigated in the meta-analysis (>15 years). Furthermore, excessive body weight drives morbidity; therefore patients attending a general practitioner are likely to be more obese than those sampled from the general population. Interestingly, abdominal obesity (diagnosed based on widely accepted waist circumference thresholds \(^2\)) was much more prevalent in women than in men. This finding suggests that the gender-specific cut-off points (102 cm in men, 88 cm in women) of current guidelines \(^3\) (pertinent to North American population) may not be most appropriate in Eastern European populations. This important epidemiological finding warrants further investigation.

We have found that all four assessed obesity measures correlated very well with CAD in age-adjusted/gender-adjusted models, and that of the four analysed anthropometric measures waist/height\(^2\) showed the best and most stable correlation with CAD. Indeed, only waist/height\(^2\) retained a significant association with CAD in men after adjusting for multiple cardiovascular risk factors. Generally, the superiority of waist/height\(^2\) was more apparent in men than in women, although females exhibited a better overall association between CAD and obesity.

There is strong epidemiological evidence that abdominal obesity is a better predictor for cardiovascular disease than overall obesity. Therefore, current guidelines recommend waist circumference as a tool to assess cardiovascular risk. \(^12\)\(^ 17\) A large multi-ethnic case-control study conducted by Yusuf et al. showed that waist/hip ratio may be superior to both BMI and waist circumference in predicting myocardial infarction, at least in men. \(^2\) Unfortunately, the protocol of our study did not include hip measurements; therefore we cannot directly compare waist/height\(^2\) against waist/hip ratio in the context of CAD. Interestingly, unlike in Yusuf's study indexing by height increased the prognostic power of waist circumference in our cohort. This finding is in concordance with a recently published large meta-analysis in which waist/height (not waist/hip ratio) was the best overall discriminator for cardiovascular diseases in both men and women. \(^7\) Moreover, consistent with these data, our study showed that obesity markers were stronger CAD correlates in women than in men. Finally, a slight superiority of waist/height over waist/hip ratio as an associate of cardiovascular events was recently reported in both the (male) Physicians Health cohort and the (female) Women's Health study. \(^10\) However, none of these investigations included waist/height\(^2\) indices. To our knowledge, waist/height\(^2\) has not been analysed before on a scale comparable to our study.

The observation that waist/height\(^2\) may be a better correlate of CAD than waist/height is first of all an empirical one. It is intuitive that "normal" waist circumference is dependent on body stature; however, there are few data on the correlation of "normal" waist circumference with body height. The analogy of waist/height\(^2\) with body mass index is obvious, although we are aware of the fact that body weight (as used for BMI calculation) relates to a mass that reflects a (three-dimensional) volume, while waist circumference is a (one-dimensional) length. Nevertheless, body weight is neither ideally indexed to cubic

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Association between coronary artery disease and four measures of obesity—age-adjusted and gender-adjusted regression analysis</th>
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</thead>
<tbody>
<tr>
<td>Both genders</td>
<td>Tertile 2 (vs 1)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.32 (1.19 to 1.46)</td>
</tr>
<tr>
<td>Waist</td>
<td>1.32 (1.19 to 1.47)</td>
</tr>
<tr>
<td>Waist/height</td>
<td>1.42 (1.28 to 1.58)</td>
</tr>
<tr>
<td>Waist/height(^2)</td>
<td>1.47 (1.32 to 1.64)</td>
</tr>
</tbody>
</table>

| Men | Tertile 2 (vs 1) | Tertile 3 (vs 1) | 1 SD increase | p Value |
| Body mass index | 1.12 (0.97 to 1.30) | 1.30 (1.12 to 1.51) | 1.14 (1.07 to 1.21) | <0.001 |
| Waist | 1.23 (1.05 to 1.43) | 1.51 (1.31 to 1.75) | 1.15 (1.08 to 1.22) | <0.001 |
| Waist/height | 1.38 (1.18 to 1.62) | 1.65 (1.42 to 1.93) | 1.19 (1.12 to 1.26) | <0.001 |
| Waist/height\(^2\) | 1.41 (1.20 to 1.65) | 1.79 (1.53 to 2.10) | 1.20 (1.13 to 1.28) | <0.001 |

| Women | Tertile 2 (vs 1) | Tertile 3 (vs 1) | 1 SD increase | p Value |
| Body mass index | 1.28 (1.12 to 1.48) | 1.78 (1.56 to 2.04) | 1.30 (1.23 to 1.36) | <0.001 |
| Waist | 1.51 (1.31 to 1.75) | 1.90 (1.65 to 2.19) | 1.28 (1.21 to 1.34) | <0.001 |
| Waist/height | 1.69 (1.46 to 1.95) | 2.12 (1.84 to 2.44) | 1.30 (1.24 to 1.38) | <0.001 |
| Waist/height\(^2\) | 1.53 (1.32 to 1.77) | 1.99 (1.73 to 2.29) | 1.31 (1.24 to 1.38) | <0.001 |

| Odds ratios (95% CI) for coronary artery disease across tertile distribution of four obesity measures and per SD increase were derived from logistic regression models including age and gender (where applicable). p Values are given for 1 SD increase in each obesity measure. |
height, nor is waist circumference optimally indexed to linear height. Whether the observed differences between different markers of obesity are clinically important remains to be elucidated. All assessed measures of obesity are highly significant discriminators of CAD, and the differences between them are minimal. Nevertheless, given the accumulating evidence for the superiority of waist circumference-derived measures of obesity over BMI for assessing CV risk, we propose that waist indexed to either height or height² should be promoted for the assessment of cardiovascular risk. In this context, waist/height and waist/height² have the practical advantage that they do not require hip measurements, which facilitates self-assessment.

Our data also reveal that men and women differ in terms of the type of obesity that shows the strongest association with CAD. While a combination of increased BMI and high waist circumference is the expected strongest anthropometric associate of CAD in women, a surrogate of sarcopenic obesity (high waist circumference with low BMI) augments risk for CAD stronger than simple obesity in men. This finding became obvious only after multivariate adjustment indicating that sarcopenic obesity is less correlated with traditional risk factors than ordinary overweight/obesity in men. Future prospective studies are warranted to elucidate the precise pathophysiological mechanisms behind this sexual dimorphism.

We are aware of several limitations of our study. First, the lack of hip measurements did not permit us to compare waist/height ratio in terms of association with CAD. Second, because of the large scale character of this cross-sectional study CAD diagnosis was based on the available medical documentation (such as ECG, angiography, stress testing) rather than strict pre-specified criteria. A uniform confirmation of the disease status through, for example, coronary angiography would certainly increase the precision of the clinical definition but was simply not feasible owing to logistic and financial constraints. Nevertheless, physician-based diagnosis of CAD has been used in several large-scale epidemiological surveys and accepted as a crude enough measure of this cardiovascular phenotype.16–21 We have no reason to believe that the pragmatic diagnosis of CAD made by 700 primary care physicians introduces a relevant systematic bias into our analyses. Third, as the phenotyping protocol did not include history of previous smoking, we were not able to adjust for this confounder. However, using information on current smoking status, and looking at current smokers and non-smokers separately, we found similar results in both groups as in the entire cohort (data not shown). Therefore, we can assume that smoking does not confound the relation of the assessed obesity parameters with CAD. Finally, the cross-sectional design of this observation study does not permit to assign the causative nature to the identified associations.

CONCLUSION
In summary, this cross-sectional study reveals an epidemic of overweight, obesity and abdominal obesity in a large population sample from Eastern Europe. It also suggests that current thresholds of waist circumference may lead to an over-estimation of abdominal adiposity prevalence in women in this population. We confirm consistently positive, graded associations between four measures of adiposity and CAD and propose waist/height squared as a novel clinically useful marker of obesity for prediction of cardiovascular risk. Moreover, we demonstrate that the associations between CAD and obesity exhibit a strong sexual dimorphism.

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