Differential Association of Anthropometric Parameters with Coronary Risk in Women – Data of the CORA Study

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Keywords

Weight gain · Waist circumference · Waist-to-hip ratio ·
Central obesity · Coronary heart disease ·
Metabolic syndrome

Summary

Objective: The predictive value of weight gain, BMI, waist circumference (WC) and waist-to-hip ratio (WHR) as to cardiovascular risk factors and coronary heart disease (CHD) is still controversial. **Methods:** 200 consecutive pre- and postmenopausal women with incident CHD (cases) were compared with 255 randomized age-matched population-based controls recruited from corresponding neighborhoods of Hamburg between 1997 and 2001. **Results:** At the time of recruitment cases and controls did not differ in BMI, but at any BMI in WC and WHR. Both parameters of central obesity were related to coronary risk. However, after adjustment for conventional risk factors, the odds ratio of WC for CHD lost its significance while the odds ratio of WHR was still 2.20 per 0.1 unit (95% confidence interval 1.48–3.27; $p = 0.0001$). The pattern of weight gain differed considerably in women with $\text{WHR} \geq 0.85$ or < 0.85 and closely matched that of women with or without CHD. The dietary pattern did not distinguish women with elevated WC or WHR. **Conclusion:** In women, an elevated WHR was closely associated with the risk for CHD independent of BMI and conventional risk factors over and above an elevated WC. An increased WC predominantly seems to reflect the presence of components of the metabolic syndrome.

Introduction

Overweight and obesity are a dramatically growing public health problem and supposed to account in great part for the increasing rates of atherosclerotic vascular disease [1, 2]. Particularly central or visceral obesity carries a risk for coronary heart disease (CHD) [3]. In industrialized countries the average waist circumference (WC) has increased more than predicted by the gain of BMI during the last centuries, particularly in women [4]. However, the results of recent studies are still ambiguous as to the differential predictive values of BMI, weight gain, WC, and waist-to-hip ratio (WHR) for coronary risk [3–6].

Data of the Framingham study suggest that BMI and even WC may misclassify individuals in terms of visceral adipose tissue and metabolic risk [7]. From data of the Physicians' Health Study and the Women's Health Study it was concluded that higher levels of adiposity – however measured – confer increased risk of CHD although WHR showed the strongest association with CHD [8]. Still, in the National Health and Nutrition Examination Survey (NHANES) WC maintained a stronger association with cardiovascular disease risk factors than other measures of adiposity [9]. A recent meta-analysis found WHR to be the best predictor for various cardiovascular risk factors, but raised the question if this holds true for cardiovascular disease as well [10].

In terms of total mortality data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study demonstrated that the use of WC and WHR in addition to BMI add further information [11]. A recent European study found a similarly predictive value of BMI, WC, and WHR in men, which was attenuated and even vanished for WC after adjustment. However, this may not hold true for women [5].

Table 1. Baseline characteristics of participants of the CORA-Study^{a,b}

Clinical characteristics	Cases (n = 200)	Controls (n = 255)	p value
Age, years	64.0 ± 9.8	64.5 ± 10.1	n.s.
Postmenopause, %	88.5	85.9	n.s.
Age at menopause, years	48.5 ± 3.3	48.5 ± 3.3	n.s.
Acute myocardial infarction, %	57	0	
Other diagnoses of CHD, %	43	0	
BMI, kg/m ²	26.2 ± 4.8	25.6 ± 4.3	n.s.
Waist circumference, cm	91 ± 13	84 ± 11	<0.0001
Waist-to-hip circumference	0.88 ± 0.09	0.82 ± 0.07	<0.0001
Height, cm	163.4 ± 6.3	163.5 ± 6.6	n.s.
Hip circumference, cm	103.5 ± 11.2	102.9 ± 10.1	n.s.
Prevalent hypertension, %	88	57	<0.0001
Prevalent type 2 diabetes, %	24	7	<0.0001
Type 2 diabetes or insulin resistance (HOMA-IR ≥ 3.8), %	58	21	<0.0001
LDL cholesterol > 3.4 mmol/l (>130 mg/dl), %	54	59	n.s.
HDL cholesterol < 1.3 mmol/l (<50 mg/dl), %	51	19	0.0001
Lipoprotein(a) > 250 mg/l, %	44	25	0.0001
Metabolic syndrome, %	70	42	<0.0001
Current smokers, %	41	29	0.01
Physical activity, h/week	0.4 ± 1.0	0.7 ± 1.0	<0.05
Meat and meat products, g/day	98.8 ± 43.6	71.9 ± 41.4	<0.0001
Fruit and vegetables, g/day	200.7 ± 85.5	250.6 ± 114.7	<0.0001

^aA case-control study of women with incident coronary heart disease and age-matched controls from the same neighborhood.

^bAnthropometric, clinical, biochemical and lifestyle characteristics are presented as percentage or mean of cases or controls ± standard deviation.

Also, weight gain during adulthood may contribute to future coronary risk [12]. This prompted us to investigate the association of body weight, weight gain, WC, and WHR with major dietary patterns, cardiovascular risk factors, and incident coronary heart disease by analyzing data of the Coronary Risk Factors for Atherosclerosis in Women (CORA) study.

Material and Methods

Design and Recruitment

The CORA study is a case-control study of 200 consecutive women aged 30–80 years, who were admitted to the University Hospital Hamburg-Eppendorf between 1997 and 2001 with the first manifestation of CHD defined as first acute myocardial infarction or first episode of angina or other symptoms suggesting coronary artery disease (ICD-10 I20, I21, and I24). Patients were excluded if CHD was not verified by angiography, if CHD had been diagnosed previously, if they had had dietary advice regarding CHD, or if they suffered from malignant or severe chronic disease. The participation rate of eligible cases was 100%. For each case two age-matched controls were randomly selected from the same neighborhood and invited through the population registry. Of 379 eligible controls 124 (33%) did not participate for various reasons, and 255 (67%) controls were included. The study protocol was approved by the ethical committee of Hamburg and conducted according to the principles of the ‘Declaration of Helsinki’. Written consent was obtained from each participant.

Data Collection

Identification of cases was undertaken everyday including weekends to prevent selection bias and to ensure blood sampling within 24 h of onset

of symptoms in cases of acute myocardial infarction. Information on socio-demographic characteristics, lifestyle, weight development, medication and family history of cardiovascular disease and the intake frequency and portion size of 146 food items eaten during the preceding year were obtained by validated questionnaires and a computer-assisted interview as used by the EPIC study [13]. All interviews and physical examinations were performed by the same trained investigator. Routine laboratory parameters were determined by standard techniques, low-density lipoprotein (LDL) cholesterol was measured by the Friedewald formula.

Type 2 diabetes mellitus was defined by use of antidiabetic medication or a history of diabetes. Blood pressure was measured in a sitting position three times after the interviews. The results of the second and third measurement were averaged [14]. Hypertension was defined by use of anti-hypertensive drugs or blood pressure ≥140/≥90 mm Hg. In nondiabetic patients a homeostasis model assessment insulin resistance (HOMA-IR) score ≥ 3.8 was categorized as insulin resistance [15]. Smokers were defined as current cigarette smokers and former smokers who stopped smoking within the last 2 years, since previous studies indicated that much of the coronary risk attributable to smoking disappears within 2 years of quitting [16, 17]. Women were defined as postmenopausal if they have had no regular monthly period for more than 1 year or were on hormone replacement therapy.

Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively; BMI was calculated as BMI = weight (kg) / height (m)². WC was measured in the middle between the lower rib margin and iliac crest, and the hip circumference (HC) was determined over the greater trochanters. Central obesity was defined by either a WHR ≥ 0.85 or a WC ≥ 80 cm [18]. Long-term weight development was assessed by recalled body weight at age 20, 30, 40, 50, 60, and 70 years using the validated questionnaire of the EPIC study [19]. Past BMI was not calculated because of the possibility of declining height during adult life. Analysis is

Fig. 1. BMI versus **a** WC ($p < 0.001$) or **b** WHR ($p < 0.0001$) of women with incident CHD (cases) and age-matched controls. WC: difference 5.4 cm, 95% CI 4.2–6.6; $p < 0.0001$; WHR: difference 0.06 units, 95% CI 0.04–0.07; $p < 0.0001$.

based on 196 cases and 253 controls for whom information on long-term weight development was available. The definition of the metabolic syndrome was adapted to the criteria of the International Diabetes Federation [20].

Statistical Analyses

Data were analyzed by using the chi-square test for frequency tables and the Wilcoxon's test for comparing arithmetic means between two groups. Analyses of variables in several subgroups were performed by analyses of variance (ANOVA). If preconditions of normal distribution were not given, calculations were performed with log data. To estimate relative risks, clinical relevant factors were entered into logistic regression analyses. Significances of associations were determined by using two-sided Pearson correlation. Statistical calculations were performed running SPSS software package version 13.0 (SPSS, Chicago, IL, USA).

Results

Conventional risk factors, including smoking, type 2 diabetes, insulin resistance, low high-density lipoprotein (HDL) cholesterol and hypertension, and thus the metabolic syndrome were more prevalent in women with CHD (cases) than in the age-matched controls (table 1). Women with CHD also had a higher intake of meat and meat products as well as a lower

intake of fruit and vegetables and were characterized by less physical activity (table 1).

Mean body weight and BMI of cases did not differ from that of controls (table 1), though obesity ($\text{BMI} > 30 \text{ kg/m}^2$) was slightly, but not significantly more prevalent in cases compared to controls (22 vs. 16%). Notably, 51% of cases and controls had a BMI of $< 25 \text{ kg/m}^2$. In contrast, cases were significantly more often affected by central obesity than controls, whereas the mean HC did not differ between both groups. Even in cases under the age of 50 years, mean WC and WHR were higher as compared to controls (WC 88 cm vs. 76 cm, $p < 0.001$; WHR 0.87 vs. 0.79, $p < 0.001$). However, the prevalence of an elevated WHR discriminated cases and controls considerably better than the WC (WHR ≥ 0.85 : 65% vs. 26%, $p < 0.0001$; WC ≥ 80 cm: 78% vs. 64%, $p < 0.0001$). Remarkably, at any BMI cases had a higher WC and a higher WHR compared to controls (fig. 1).

Women with diabetes or insulin resistance, hypertension, low HDL cholesterol, or a metabolic syndrome reported a lower intake of fruit and vegetables ($p < 0.05$ for each, hypertension n.s.) and a significantly higher intake of meat and meat products compared to those without these characteristics (for each $p < 0.0001$). Both, WC and WHR correlated similarly with a higher intake of meat and meat products and a lower intake of fruit and vegetables (fig. 2).

Cases and controls, who had developed diabetes or insulin resistance, hypertension or a low HDL cholesterol – most of whom were among the cases –, had continuously gained significantly more weight than women without these characteristics (fig. 3a–c). A similar substantial weight gain was observed in women with metabolic syndrome in contrast to those without metabolic syndrome (fig. 3d). Weight development did not differ between women with an LDL cholesterol $> 130 \text{ mg/dl}$ or cholesterol-lowering medication and those with an LDL cholesterol $\leq 130 \text{ mg/dl}$.

Comparable to women with risk factors, women with a WC ≥ 80 cm reported a substantial continuous weight gain of more than 10 kg over time while women with a WC < 80 cm had been able to control their weight within narrow bounds between 20 and 60 years of age (fig. 4a). In contrast, both women with or without elevated WHR reported an average weight gain of 10 kg since the age of 20 years. However in women with an elevated WHR the major weight gain occurred about 10 years earlier compared to women with a normal WHR (fig. 4b). This pattern of weight gain in early age of women with or without an elevated WHR closely matched that of women with or without incident CHD (fig. 4c).

Weight gain between 30 and 40 years correlated most strongly with a WHR ≥ 0.85 at recruitment ($p < 0.0001$) and likewise with incident coronary events ($p < 0.0001$). Every increase of 1% of body weight between 30 and 40 years of age was associated with a 3% increase of risk for developing a WHR ≥ 0.85 (odds ratio 1.034, 95% confidence interval (95% CI) 1.012–1.057; $p < 0.002$), and likewise a 3% rise of coronary

Fig. 2. Association between the intake of meat and meat products or fruit and vegetables with **a** WC or **b** WHR in women. The trend lines of fruit and vegetables include 8 subjects with an intake between 500 and 700 g/day and one subject with an intake of 928 g/day, which are not shown. The dotted lines indicate the 95th percentile confidence interval. Coefficients of determination and two-sided Pearson correlation: WC versus fruit and vegetables: $R^2 = 0.0174$, $p = 0.005$, and versus meat and meat products: $R^2 = 0.0977$, $p < 0.0001$; WHR versus fruit and vegetables: $R^2 = 0.0132$, $p = 0.015$, and versus meat and meat products $R^2 = 0.0706$, $p < 0.0001$.

risk (odds ratio 1.03, 95% CI 1.007–1.050; $p < 0.008$). After adjustment for previously identified clinical relevant risk factors, including smoking, lipoprotein(a), hypertension, low HDL cholesterol, diabetes and insulin resistance, these observations lost their significance, indicating that weight gain predominantly reflects development of conventional risk factors.

Both parameters of central obesity, WC and WHR, were positively associated with the risk of CHD. The unadjusted odds ratio was for a higher WC and an elevated WHR 1.56 per 10 cm (95% CI 1.33–1.84; $p < 0.0001$) and 3.47 per 0.1 unit (95% CI 2.45–4.92; $p < 0.0001$), respectively. However, after adjustment for smoking, hypertension, low HDL cholesterol, diabetes and insulin resistance, and elevated lipoprotein(a), the odds ratio of WC was attenuated and lost its significance. In contrast, when HC was added to the multivariate model,

the odds ratio of WC regained significance (2.11 per 10 cm, 95% CI 1.42–3.13; $p < 0.0001$). Correspondingly, the odds ratio of WHR adjusted for the conventional risk factors remained highly significant (adjusted odds ratio 2.20 per 0.1 unit, 95% CI 1.48–3.27; $p = 0.0001$). Adjusting for height or using waist-to-height ratio and WHR-to-height ratio did not change the results of the multivariate analyses in this study.

Discussion

This analysis of the CORA study indicates that WC and WHR may differ in their information as to cardiovascular risk in women. An elevated WC appears to reflect long-term continuous weight gain, associated with the development of

Fig. 3. Weight development during adult life in women with or without **a** hypertension, **b** diabetes or elevated HOMA-IR score, **c** low HDL cholesterol, or **d** metabolic syndrome. Data of cases and controls were combined since the weight development was similar. Naturally more cases than controls were affected by risk factors. (mean weight $\pm$ 95% CI; differences of trends $p < 0.0001$).

conventional risk factors while an elevated WHR is strongly related to incident CHD over and above the effect of components of the metabolic syndrome. Moreover, the results of the CORA study suggest that weight gain in early adulthood may induce a rise of WHR and likewise of coronary risk in women.

The results of the CORA study are in line with data from NHANES which has identified BMI as an insufficient measure of metabolic health or disease, since a large proportion of participants with normal weight were metabolically abnormal while a large proportion of overweight and obese individuals are metabolically healthy [6]. In the CORA study, cases and controls differed much more in WHR than in WC. Misclassification by BMI and even WC was also reported from the Framingham study [7]; in a recent meta-analysis, the WHR was more strongly associated with CVD although the difference was not significant [3].

On average women, whether cases or controls, had gained 10 kg of weight. However, women with a WC ≥ 80 cm or with components of the metabolic syndrome at the age of the manifestation of CHD reported a higher weight by the age of 20 years which suggests an onset of weight gain during adolescence that continues through adulthood while weight of those with normal WC or without conventional risk factors started lower and remained more or less stable. Thus, in preventive medicine it is not sufficient to focus on the absolute weight, but one should also pay attention to the individual weight gain during adolescence and adulthood. It is of note that 51%

of the cases were not overweight, and of the cases with a WC ≥ 80 cm about one third were still in the range of normal weight, lately termed 'normal weight obesity'. In other studies [21–24], higher initial weight with continuous weight gain also has been reported for patients with hypertension, glucose intolerance, diabetes, low HDL cholesterol, and the metabolic syndrome. A dietary pattern characterized by a high intake of meat and meat products and a lower intake of fruit and vegetables may be critical [25].

However in the CORA study the pattern of weight gain associated with components of the metabolic syndrome appears to differ from that related to CHD which is characterized by an early weight gain particularly between 30 and 40 years of age. Most interestingly this pattern of weight development in early adulthood closely matches that of women with an elevated WHR. Thus, early weight gain may lead to a rise of WHR and likewise of coronary risk. These findings of the CORA study are supported by a number of observational studies, demonstrating that early weight gain and obesity before middle age promotes atherosclerosis in men and women and is associated with a reduction of life expectancy, years lived free of CHD, or higher risk of hospitalization and mortality from CHD [2, 12, 26–28]. Thus, avoiding early weight gain should be a prime goal of cardiovascular prevention in women.

A clinically relevant finding of the CORA study is certainly that an elevated WC is associated with components of the

Fig. 4. Weight development during adult life **a** in women with normal or elevated WC ($p < 0.0001$), **b** in women with normal or elevated WHR ($p < 0.0001$), or **c** in women with incident CHD (cases) and age-matched controls (b) (p between 30 and 40 years < 0.0001). Mean weight $\pm 95\%$ CI; p values indicate significant differences of trends.

metabolic syndrome while an elevated WHR is strongly related to incident CHD over and above conventional risk factors. This leaves the interesting question as to the nature of the additional factors reflected by WHR that contribute to the cardiovascular risk. HC probably adjusts for subcutaneous adipose tissue and general adiposity but may also reflect trained gluteal musculature as a measure of physical fitness, particularly in lean individuals [29]. Yet, future research may reveal additional as yet undetermined confounders that may add to the impact of WHR, which are not covered by WC. Interestingly, in the CORA study women with CHD were characterized by less physical activity compared to controls (table 1), particularly below the age of 60 years (data not shown). In line with the latter hypothesis, the data of the CORA study do not point to differences in dietary patterns that may lead to higher WC versus higher WHR.

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The study has limitations that need to be addressed. One is certainly recalled body weight, even though recorded with the validated questionnaire of the EPIC study [19]. Most data show trends of underreporting for weight although the degree varies between populations examined [30]. First, self-reported information on weight in an adult population seems to be mainly influenced by age and body weight. In the CORA study, cases and controls were age-matched, and the proportion of overweight participants was similar in both groups. Secondly, women tend to underestimate weight with the exception of those with high school education [31]. In the CORA study, less cases than controls had a high school education. Thus, if anything, the difference between cases and controls may be underestimated. Also, information on long-term weight development was available from 98% of the cases and 99% of the controls, and a systematic error should be balanced between cases and controls in any case.

Conclusions

In this analysis of the CORA study on German women an elevated WHR was closely associated with the risk for CHD, independent of BMI and conventional risk factors over and above of an elevated WC. An increased WC seemed to predominantly reflect components of the metabolic syndrome. Both parameters of central adiposity are associated with weight gain, yet, elevated WHR and CHD later in life are preceded specifically by early weight gain. Thus, for women a central goal in cardiovascular prevention may be the avoidance of early weight gain.

Acknowledgements

We are indebted to all participants of the study for their collaboration. We also thank Ms. E. Kohlsdorf and W. Bernigau from the German Institute of Nutrition for their expert biomathematical assistance. Financial support of the CORA study was primarily given by the German Stifterverband für die Wissenschaft.

Disclosure Statement

Competing financial interests of all authors have been appropriately disclosed according to the policy of the journal. No competing financial interests exist.

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