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Accuracy of anthropometric indicators of obesity to predict cardiovascular risk

Obesity and cardiovascular risk

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Abstract

CONTEXT Obesity is associated with various cardiovascular risk factors. The body mass index (BMI) is the standard measure of overweight and obesity. More recently, however, waist-to-hip ratio (WHR) or waist circumference (WC) as more sensitive measures for visceral obesity, have been proposed to be more inidicative of cardiovascular risk.

OBJECTIVE This study was performed to test the predictive value of anthropometric parameters for the presence of several cardiovascular risk conditions

DESIGN The DETECT study is a cross-sectional, clinical-epidemiological study.

PARTICIPANTS We studied 5,377 unselected subjects (2,016 men, 3,361 women) without arteriosclerotic disease, aged 20-79 years, from the DETECT laboratory sample.

SETTING Primary care.

INTERVENTION We measured anthropometric parameters and assessed cardiovascular risk by clinical examination, patient history, and a standardized laboratory program.

MAIN OUTCOME MEASURES We assessed the associations of BMI, WC, hip circumference, WHR and waist-to-height ratio (WHtR) to cardiovascular risk by calculating the area under the receiver-operating characteristics (ROC) curve and adjusted odds ratios for metabolic syndrome, dyslipidemia, and type 2 diabetes.

RESULTS The area under the ROC curve for WHtR was significantly higher than for all other anthropometric parameters with respect to all risk conditions in women and to dyslipidemia and type 2 diabetes in men. The odds ratios for presence of risk conditions with one standard deviation increase of each anthropometric parameter were highest for WHtR or WC.

CONCLUSIONS There are some indications that WHtR or WC may predict prevalent cardiovascular risk better than BMI or WHR even though the differences are small.

Introduction

Obesity is a major risk factor for the development of chronic diseases and mortality (1-3). The risk of cardiovascular events rises with increasing body mass index (BMI) (4). The WHO recommends measurement of the BMI as a universal criterion of overweight (>= 25) and obesity (>= 30) while also measures of abdominal fat distribution such as waist circumference (WC) or waist-to-hip ratio (WHR) are encouraged (5). Prospective epidemiological studies have shown increased abdominal fat accumulation to be an independent risk factor for type 2 diabetes mellitus and cardiovascular risk conditions, such as coronary artery disease (CAD), stroke, and hypertension (6-8). Visceral fat accumulation is associated with increased secretion of free fatty acids (FFA), hyperinsulinemia, insulin resistance, hypertension, and dyslipidemia (reviewed in 10,11). The WHR as a measure of abdominal fat accumulation has been shown to be a better predictor of cardiovascular risk than BMI (6-9). Other authors have promoted the WC and two different cut-offs for WC have been proposed based on data derived from population based studies (94 or 102 cm for men, and 80 or 88 cm for women, respectively) (12,13). The upper levels have been adopted by the National Cholesterol Education Program (NCEP) and the use of the term metabolic syndrome has been suggested to identify the common cluster of metabolic abnormalities, defined as three or more of five criteria: 1) abdominal obesity (waist circumference, >102 cm in men and >88 cm in women), 2) hypertriglyceridemia [>=1.69 mmol/liter (>=150 mg/dl)], 3) low HDL <1.04 mmol/liter (<40 mg/dl) in men and <1.29 mmol/liter (<50 mg/dl) in women], 4) hypertension (>=130/85 mm Hg), and 5) elevated fasting glucose [>=6.1 mmol/liter (>=110 mg/dl)] (14). It has been shown that the hazard ratios for future coronary heart diesease or diabetes mellitus increase with the presence of each additional factor of the metabolic syndrome (15). More recently, a redefinition of the metabolic syndrome has been suggested by the International Diabetes Foundation, using adapted waist circumferences for different ethnic groups (16). Based on this new definition, in the USA, a higher prevalence of the metabolic syndrome than previously estimated was found (17). The WC has also been shown to correlate well with area of visceral fat mass assessed with MRI (18).

However, the WC has been criticized for not taking into account differences in body height and the ratio of WC to height (waist-to-height ratio, WHtR) has been proposed as a better predictor of cardiovascular risk (19,20), mortality (21), and intra-abdominal fat (22). In a population-based study from Hong-Kong, this ratio has been found to be most strongly associated to cardiovascular risk when using receiver-operating characteristics (ROC) analysis and a cut-off of 0.5 has been suggested for an Asian population (23). We have recently shown in a large cohort of primary care patients from the DETECT study that the WHtR predicts point prevalence of CAD, type 2 diabetes, and dyslipidemia, as assessed by physicians' records, better that other measures of obesity. Hypertension, however, was best predicted by BMI (20).

In this study we aimed at comparing the association of the anthropometric measures WHR, hip circumference (HC), WC, BMI, and WHtR with the presence of the metabolic syndrome, hypertension, and type 2 diabetes in a large primary-care sample with a standardized laboratory assessment and physical examination.

Methods

Subjects and Design

Design:

DETECT is a cross-sectional study of 55.518 unselected consecutive patients (59% women; over 17 years) in 3.188 primary care offices in Germany including a prospective substudy in a random subset of 7.519 patients, characterized additionally by an extensive standardized laboratory program (24). For participation in the standardized laboratory program, 1000 randomly selected doctors were asked to participate. Of these, 149 doctors dropped out, leaving 851 doctors participating in the laboratory program. By comparing the finally participating doctors to a pre-study questionnaire, they were found to be nationally representative in terms of regional distribution, age, years of experience, specialty orientation, and patient load per day (24).

Patients

The study was approved by the local ethics committee and all patients gave written informed consent. During a specified half day, all patients attending the primary care practice were asked to participate in the study. We did not record ethnicity but, being representative of the German population, the patients were mainly of Caucasion ethnicity. To clearly define cardiovascular risk conditions we only included patients from the subset with the standardized laboratory program in this study. Patients with known coronary artery disease, peripheral artery occlusion, carotid stenosis, or stroke, age <= 20 or > 79 years, and lack of complete anthropometrical data of were excluded. Thus, 5,377 patients (2,016 men, 3,361 women) were finally analyzed in this study. For the definition of the metabolic syndrome, we additionally excluded patients with type 2 diabetes or intake of medications used to lower tryglicerides (nicotinic acid derivates, fibrates) leaving 4,585 patients (1,636 men, 2,949 women) for this analysis.

Instruments and measures:

All diagnoses were recorded by the primary care physicians. Physician's diagnoses were classified as definite, possible or not present and current medication was recorded. In case of diabetes, type 1 or type 2 was indicated. Laboratory values, obtained in the central laboratory in Graz were used for risk assessment. Doctors were advised to measure weight, height, blood pressure, and waist and hip circumferences according to written, standardized instructions given in a manual. Systolic and diastolic blood pressure was measured by indirect cuff sphygmomanometry after several minutes of rest in sitting position. Use of an appropriate cuff size was advised. WC was measured with a tape measure midway between the lowest rib and the pelvis, HC was measured at the widest circumference of the hip. The following anthropometric parameters were calculated: BMI (weight in kg divided by the square of height in meters); WC (in cm); HC (in cm); WHR: WC divided by HC; WHtR (WC divided by measured height in cm).

Lipids and lipoproteins:

Blood samples were collected and shipped to the central laboratory at the Medical University of Graz (Austria) within 24 hours. Clinical chemical parameters as well as cholesterol and triglycerides were determined on a Roche Modular automatic analyzer. Lipoproteins (HDL, LDL, and VLDL) were determined electrophoretically on the HELENA SAS-3 /SAS-4 system. Hemoglobin (Hb) A1c was determined chromatographically on a ADAMS HA 8160 analyzing system. For all parameters, reagents and secondary standards were used as recommended by the manufacturers. Inter-assay coefficients of variation of these methods are provided in (24).

We analyzed the associations of the anthropometric measures with metabolic syndrome, dyslipidemia, and type 2 diabetes. The variables were defined as follows for the purpose of this study:

Metabolic syndrome: presence of at least two of the following conditions: Serum triglycerides >=150 mg/dl, HDL <40 mg/dl in men and <50 mg/dl in women, measured blood pressure >=130/85 mmHg, and fasting blood glucose >=110 mg/dl.

Dyslipidemia: LDL cholesterol levels above the target values defined by the NCEP risk categories I-III or if there was a clinical history of dyslipidemia (physician's diagnosis or being on lipid-lowering medication). Risk category I: 0 or 1 NCEP risk factor, Risk category II: 2 or more NCEP risk factors, or 10 year risk ≤ 20%, risk category III: 10 year risk > 20% or a diagnosis of CHD or previous stroke or symptomatic carotid stenosis or peripheral arterial disease. NCEP risk factors were: Cigarette smoking, hypertension (BP≥140/90 mmHg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CAD (CAD in male first-degree relative <55 years; CAD in female first-degree relative <65 years), age (men ≥45 years; women ≥55 years) (14).

Type 2 diabetes: Definite physician's diagnosis of type 2 diabetes or oral antidiabetic intake or insulin therapy, exclusion of patients with diagnosis of type 1 diabetes.

Confounding conditions were assessed by patients' history, laboratory examination, or physical examination. Specifically, the conditions were defined as follows: smoking status: patients' history of previous or current smoking; physical activity: patients' history of physical activity > 2 hours/week; and hypertension: measured blood pressure <=140/90 mmHg.

Statistical analyses

Patients were analyzed separately by sex, for all age groups and by three age groups (20-44, 45-65, 66-79 years). Additionally we analyzed the high-risk age groups as defined by the NCEP (14) with the ages of 35-65 years and 45-75 years in men and women, respectively. Sensitivity and specifity were examined by receiver-operating characteristics (ROC) analysis and the areas under the ROC curves (AUC) were calculated for each anthropometrical parameter and each risk condition. Individual cut-offs were defined as that point on the curve where the sum of sensitivity and specifity was highest. Differences between AUCs were tested with a non-parametrical test (25). Additionally, we calculated adjusted odds ratios (OR) by applying logistic regression models of the different conditions in case of an increase of one standard deviation (SD) of the respective anthropometric parameter. Statistical inference is based on 95%

confidence intervals and 5% P-Values, respectively. These estimates were calculated by the Huber-White-Sandwich Matrix (26) to account for the clustered structure (clusters: primary care settings) of the sample. All statistical analyses were conducted with the software package STATA 9.2 (Stata Corp., College Station, TX, USA).

Results

Table 1 summarizes the prevalences of metabolic syndrome, dyslipidemia and type 2 diabetes. The prevalences were weighted for regional distribution of the total sample. The prevalence of the three risk conditions was higher in men than in women and the prevalences increased with age groups in both genders.

The AUC of the ROC analyses are shown in table 2. The AUC is a measure of the degree of separation between affected and non-affected subjects by a specific test. An AUC of 1 indicates perfect separation between affected and non-affected subjects and an AUC of 0.5 indicates no discriminative value of the test used. Regarding dyslipidemia and type 2 diabetes, the AUC for the WHtR were significantly higher than for the other anthropometric parameters in both sexes. Additionally, the AUC for WHtR was significantly higher regarding metabolic syndrome only in women. In the high-risk age groups (men 35-65 years, women 45-75 years), there were significant differences for dyslipidemia in both sexes. Separate analyses of the age groups 20-44, 45-65, and 66-79 years revealed no further significant differences (data not shown). Table 3 displays the calculated cut-off levels and the respective sensitivities and specifities.

Figure 1 shows the OR for the different risk conditions for a 1 SD increase of the respective anthropometric parameters after adjustment for a) age, b) age, smoking status, physical activity, family history of type 2 diabetes, dyslipidemia, and hypertension, and c) all factors and BMI (for WHtR)/WHtR (for all other anthropometric parameters). In men, the OR were highest for WHtR, followed by WC and BMI for all conditions. Women had the highest OR for WC, followed by WHtR and BMI. In both sexes, WHR had the lowest OR for all conditions.

Discussion

Here we present data of a large study examining the association of several anthropometric parameters with three distinct cardiovascular risk conditions in a primary care population. We used metabolic syndrome, dyslipidemia, and type 2 diabetes because these risk factors are associated to obesity and are independent risk factors for cardiovascular events. Additionally, cardiovascular risk accumulates with increasing numbers of factors that constitute the metabolic syndrome (15).

In the ROC analysis, WHtR proved to predict most conditions significantly better than all other anthropometric parameters. When calculating OR that allow to adjust for further influencing factors, WHtR was still a slightly better predictor in men, whereas in women, WC was slightly superior. WC has been proposed as a general measure of abdominal obesity by other authors (12,13). Possibly, the fact that WHtR takes differences in body height into account, contributes to the higher AUC of the WHtR with respect to the WC in the ROC analyses. It has been shown that WHtR is a better predictor of mortality and cardiovascular risk factors than WC (19-21).

The WHR has also been proposed as a good predictor of cardiovascular events (6-9). We found it to be most weakly associated to all risk conditions. Possibly, this is due to the fact that we have examined a high risk population with a high prevalence of morbidity and obesity. Here, the concomitant increase in hip circumference might have rendered the WHR less useful.

The hip circumference was also positively associated to most single and combined cardiovascular risk conditions. In an Australian study, surprisingly, a lower prevalence of newly diagnosed diabetes and dyslipidemia was found in subjects with higher hip circumferences (28). In a recent case-control study by Yusuf et al., higher hip circumferences were also found to be protective against myocardial infarction (9). The reason for these different results is unclear. Possibly, differences in study design (case-control vs. cross-sectional), subject populations (general population or highly selected hospitalized patients, vs. primary-care patients), statistical methods (such as adjustment for waist and other factors), definitions of conditions (newly diagnosed risk conditions vs. all patients with risk conditions), and methods of measurement of hip circumference (at the great trochanters vs. at the largest hip circumference) played a role. Moreover, in the study by Yusuf et al., patients from other hospital wards were included as controls (9). Possibly, presence of other diseases among the controls might have led to potential bias (20).

Our results of a positive, albeit less strong association of hip circumference with cardiovascular risk suggest that not only visceral fat is involved in the cardiovascular risk of obesity. It is not clear, though, whether this association is a consequence of direct detrimental effects of subcutaneous fat or, rather, an indirect effect due to the fact that hip circumference is also an indicator of overall fatness, including visceral fat. This positive association might also explain why the WHR had the weakest association to cardiovascular risk. If both waist and hip circumference are positively associated with risk factors it can be expected that the ratio of both has a weaker association. Even though, in some studies the WHR has been shown to be strongly associated with cardiovascular risk factors (6-9), it has also been criticized for masking accumulation of abdominal fat, if the hip circumference is also increased (29).

It has to be kept in mind that this is a cross-sectional study. Therefore, these findings should be interpreted against that background. Our data only show the association with present risk factors conditions but do not directly predict the future risk of cardiovascular events. Moreover, a survivor bias cannot be ruled out. It is possible that older persons with highest risk have died that could not be studied here. The association with risk factors, on the other hand, clearly points to an increased risk of future events. In order to elucidate which anthropometric parameter is the predictor of future cardiovascular events, however, prospective studies are necessary. A further limitation of our study is the fact that treating physicians only received written instructions on the anthropometric measurements. Possibly, a more detailed training would have reduced potential measurement errors. On the other hand, this study was designed to reflect every-day routine in primary care. The fact that we have found clear results shows that these anthropometric parameters can be used in daily routine and that they have a predictive value if applied in daily routine.

The WHtR has already been suggested as a common measure of central obesity for an Asian population; here, a cut-off level of 0.5 for both sexes has been recommended (23,30,31). This cut-off level has also been suggested for use in European subjects (32). Our study suggests the use of a higher cut-off (0.54-0.59). These studies differ to our study in several aspects. First, the sample number investigated there was smaller than our sample size. Second, these cut-off values have been established for an Asian population and it has been shown that cardiovascular risks are present at a lower BMI in Asians than in Caucasians (33), therefore the WHtR cut-offs for Caucasians are likely to differ as well. And, third, these studies have been conducted in the general population, whereas our study was carried out in a primary care setting. Thus, our sample is more representative of the high-risk population seen in general practice where the question of weight management often arises. Recently, the issue of ethnic differences in abdominal obesity has been adressed by a large-scale international study (34).

Taken together, our data indicate that the WHtR and, to a lesser extent the WC appears to be a better indicator of cardiovascular risk than the BMI. The WHtR is a parameter that is simple to assess. It has advantages over BMI as it is easier to calculate and to understand for lay persons (no square term is used in the formula) and less clothes need to be removed for measurement. Moreover, measures including WC are more sensitive to diet and training than the BMI as increase of muscle mass might lead to little change of BMI but clear changes in WC and WHtR. The WHR is not only more complicated to assess, it also has been shown to be a far weaker predictor of cardiovascular risk factors. Our study favors the use of an anthropometric parameter of abdominal obesity over BMI, though, further prospective studies are needed for a definite conclusion on the best predictor of future cardiovascular events.

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Figure's Legend

Figure 1:

Odds ratios for metabolic syndrome (A), dyslipidemia (B) and type 2 diabetes (C) for 1 SD increase in antropometric parameter (vertical bars=95% CIs, other risk factors=smoking status, physical activity, family history type 2 diabetes, dyslipidemia and hypertension, 1 SD Female: WHR=0.11; HC=13.96cm; WC=14.72cm; BMI=5.35; WTR=0.09; 1SD Male: WHR=0.09; HC=10.78cm; WC=12.77cm; BMI=4.27; WTR=0.08)

Table 1: Prevalence of cardiovascular risk conditions in the studied sample

	N	metabolic syndrom (N=924) %	dyslipidemia (N=2,893) %	type 2 diabetes (N=714) %
total	5,377	20.2	53.8	13.3
18-44	1,368	11.1	25.6	2.3
45-65	2,667	21.3	57.4	12.4
66+	1,342	29.9	75.0	26.2
female	3,361	16.8	48.6	11.2
18-44	919	6.7	18.8	2.0
45-65	1,597	17.7	52.0	9.5
66+	845	29.0	74.7	24.4
male	2,016	26.3	62.5	16.8
18-44	449	20.3	40.3	2.9
45-65	1,070	27.2	65.6	16.8
66+	497	31.7	75.7	29.4

Table 2: Associations of antropometric variables and metabolic syndrome, dyslipidemia and type 2 diabetes (N=5,377)

	WHR		HC		WC		BMI		WHtR	
	AUC	**95% CI**	**AUC**	**95% CI**	**AUC**	**95% CI**	**AUC**	**95% CI**	**AUC**	**95% CI**
female										
metabolic syndrome	0.62	0.60 - 0.64	0.69	0.67 - 0.71	0.72	0.70 - 0.74	0.72	0.70 - 0.73	0.73*	0.71 - 0.74
dyslipidemia	0.62	0.60 - 0.64	0.65	0.63 - 0.67	0.68	0.66 - 0.70	0.67	0.66 - 0.69	0.70*	0.68 - 0.72
type 2 diabetes	0.65	0.62 - 0.68	0.71	0.68 - 0.74	0.75	0.72 - 0.77	0.74	0.72 - 0.77	0.76*	0.74 - 0.79
female age group 45-75										
metabolic syndrome	0.61	0.58 - 0.63	0.66	0.64 - 0.69	0.69	0.67 - 0.71	0.68	0.66 - 0.71	0.69	0.67 - 0.71
dyslipidemia	0.60	0.57 - 0.62	0.61	0.59 - 0.64	0.64	0.61 - 0.66	0.63	0.61 - 0.65	0.65*	0.63 - 0.67
type 2 diabetes	0.63	0.60 - 0.66	0.69	0.65 - 0.72	0.72	0.69 - 0.74	0.72	0.69 - 0.75	0.73	0.70 - 0.76
male										
metabolic syndrome	0.59	0.56 - 0.61	0.64	0.62 - 0.67	0.67	0.64 - 0.69	0.66	0.64 - 0.69	0.67	0.65 - 0.70
dyslipidemia	0.58	0.55 - 0.60	0.60	0.58 - 0.63	0.63	0.60 - 0.65	0.62	0.59 - 0.64	0.65*	0.62 - 0.67
type 2 diabetes	0.61	0.58 - 0.64	0.67	0.64 - 0.70	0.69	0.66 - 0.72	0.69	0.66 - 0.72	0.72*	0.69 - 0.74
male age group 35-65										
metabolic syndrom	0.60	0.57 - 0.63	0.64	0.61 - 0.67	0.68	0.65 - 0.71	0.68	0.65 - 0.71	0.69	0.66 - 0.72
dyslipidemia	0.57	0.54 - 0.60	0.62	0.59 - 0.65	0.63	0.60 - 0.66	0.62	0.59 - 0.65	0.64*	0.61 - 0.67
type 2 diabetes	0.62	0.57 - 0.66	0.69	0.65 - 0.73	0.71	0.67 - 0.75	0.71	0.67 - 0.75	0.72	0.68 - 0.76

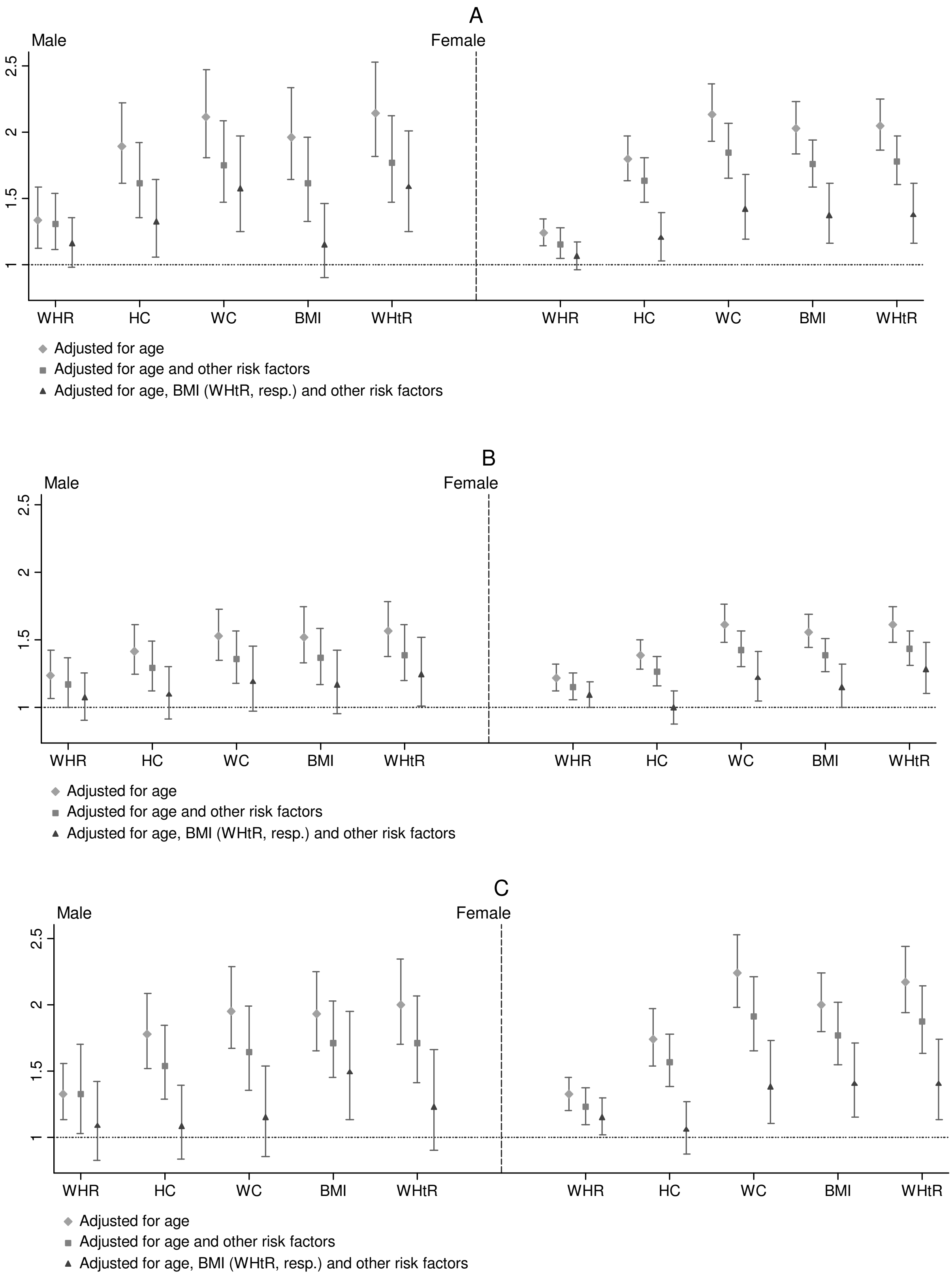
AUC=Area under Curve estimated by ROC analyses.
WHR=waist-to-hip ratio. HC=hip circumference. WC=waist circumference. BMI=body-mass index. WHtR=waist-to-height ratio.
*AUC significantly larger than next smaller AUC, significance calculated only for difference between parameters with highest and second highest AUC

Table 3: Cut-Off values, sensitivity and specificity for the association of antropometric paramters and metabolic syndrome, dyslipidemia and type 2 diabetes (N=5,377)

	WHR			HC			WC			BMI			WHtR		
	Cut-Off	**Sens**	**Spez**	**Cut-Off**	**Sens**	**Spez**	**Cut-Off**	**Sens**	**Spez**	**Cut-Off**	**Sens**	**Spez**	**Cut-Off**	**Sens**	**Spez**
female															
metabolic syndrome	>= .85	0.60	0.59	>= 104	0.64	0.66	>= 89	0.66	0.67	>= 25.8	0.66	0.66	>= .54	0.70	0.65
dyslipidemia	>= .85	0.60	0.58	>= 104	0.61	0.62	>= 89	0.63	0.63	>= 25.9	0.63	0.63	>= .55	0.63	0.67
type 2 diabetes	>= .87	0.58	0.63	>= 108	0.66	0.66	>= 94	0.68	0.67	>= 27.8	0.68	0.68	>= .58	0.70	0.68
female age group 45-75															
metabolic syndrome	>= .85	0.61	0.55	>= 105	0.63	0.63	>= 90	0.66	0.63	>= 26.3	0.64	0.64	>= .56	0.63	0.67
dyslipidemia	>= .86	0.54	0.59	>= 105	0.59	0.58	>= 91	0.58	0.62	>= 26.4	0.59	0.59	>= .56	0.60	0.62
type 2 diabetes	>= .87	0.58	0.61	>= 109	0.64	0.64	>= 96	0.65	0.67	>= 28.3	0.67	0.67	>= .59	0.67	0.67
male															
metabolic syndrome	>= .95	0.60	0.54	>= 104	0.60	0.59	>= 99	0.62	0.64	>= 26.5	0.62	0.62	>= .56	0.63	0.62
dyslipidemia	>= .96	0.54	0.59	>= 105	0.56	0.59	>= 100	0.58	0.58	>= 26.8	0.59	0.58	>= .57	0.59	0.62
type 2 diabetes	>= .97	0.58	0.60	>= 107	0.62	0.63	>= 103	0.65	0.64	>= 28.0	0.64	0.64	>= .59	0.65	0.67
male age group 35-65															
metabolic syndrome	>= .95	0.61	0.56	>= 104	0.59	0.62	>= 98	0.64	0.63	>= 26.6	0.63	0.64	>= .55	0.66	0.60
dyslipidemia	>= .96	0.54	0.60	>= 104	0.59	0.55	>= 99	0.60	0.58	>= 26.9	0.58	0.59	>= .56	0.60	0.60
type 2 diabetes	>= .97	0.62	0.61	>= 107	0.64	0.65	>= 103	0.66	0.66	>= 28.2	0.65	0.66	>= .58	0.68	0.64

Cut-Off=Estimated by the Youden-Index with equal weighted sensitivity and specificity in ROC analyses
Sens=sensitivity. Spez=specificity.
WHR=waist-to-hip ratio. HC=hip circumference [cm]. WC=waist circumference [cm]. BMI=body-mass index. WHtR=waist-to-height ratio.

Figure 1


A
Male
Female
2.5
2
1.5
1
WHR
HC
WC
BMI
WHtR
WHR
HC
WC
BMI
WHtR
Adjusted for age
Adjusted for age and other risk factors
Adjusted for age, BMI (WHtR, resp.) and other risk factors
B
Male
Female
2.5
2
1.5
1
WHR
HC
WC
BMI
WHtR
WHR
HC
WC
BMI
WHtR
Adjusted for age
Adjusted for age and other risk factors
Adjusted for age, BMI (WHtR, resp.) and other risk factors
C
Male
Female
2.5
2
1.5
1
WHR
HC
WC
BMI
WHtR
WHR
HC
WC
BMI
WHtR
Adjusted for age
Adjusted for age and other risk factors
Adjusted for age, BMI (WHtR, resp.) and other risk factors