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Original
Central adiposity markers, plasma lipid profile and cardiometabolic risk prediction in overweight-obese individuals / Barazzoni, R., Gortan Cappellari, G., Semolic, A., Ius, M., Zanetti, M., Gabrielli, A., Vinci, P., Guarnieri, G., Simon, G.. - In: CLINICAL NUTRITION. - ISSN 0261-5614. - 38:3(2019), pp. 1171-1179. [10.1016/j.clnu.2018.04.014]

Availability:
This version is available at: 11368/2935809 since: 2019-11-20T19:06:50Z
Publisher:

Published
DOI:10.1016/j.clnu.2018.04.014
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16 September 2026

arTs Università degli Studi di Trieste
Archivio della ricerca – postprint

Central adiposity markers, plasma lipid profile and cardiometabolic risk prediction in overweight-obese individuals

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ARTICLE INFO

Accepted 25 April 2018

Keywords:
Insulin resistance
Metabolic syndrome
Obesity
A body shape index
Waist circumference
Body mass index

SUMMARY

Background: Waist circumference (WC) is the currently recommended marker of central fat for cardiometabolic risk screening. Alternative surrogate markers have been recently proposed to better reflect the metabolic impact of central fat accumulation per se, based on WC normalization by height (Weight-to-Height Ratio – WtoH; Body Roundness Index – BRI) or body mass index (BMI) without (A Body Shape Index – ABSI) or with inclusion of plasma triglyceride and HDL-cholesterol concentrations (Visceral Adiposity Index – VAI).
Methods: We investigated associations between WtoH, BRI, ABSI or VAI and insulin resistance (HOMA-index) or metabolic syndrome (MetS) in a general population cohort from the North-East Italy Mo.Ma. study (n = 1965, age = 49 ± 13 years, BMI = 26.7 ± 5.2 kg/m^2). Baseline values were also evaluated as predictors of future insulin resistance and MetS in overweight-obese individuals undergoing 5-year follow-up (Ow-Ob) (n = 263; age = 54 ± 9, BMI = 30,7 ± 4,1).
Results: Compared to WC or BMI, basal WtoH and BRI were similarly associated with baseline HOMA and MetS prevalence after multiple adjustments ($P < 0.001$) and all markers similarly predicted 5-year HOMA and MetS ($P < 0.001$). Under basal conditions, superimposable results were observed for VAI whereas ABSI was less accurate or unable to identify baseline HOMA and MetS ($p < 0.05$ vs WtoH-BRI-VAI-WC-BMI). VAI had highest 5-year risk predictive value in Ow-Ob [ROC Area Under the Curve (AUC) VAI > WtoH-BRI-WC-BMI; $p < 0.05$] while no predictive value was in contrast observed for ABSI (ROC AUC ABSI < WtoH-BRI-WC-BMI; $p < 0.05$). Using alternate formulae with plasma lipid inclusion in ABSI and removal from VAI calculations completely reversed their 5-year predictive value and AUC.
Conclusions: The current findings do not support replacement of WC with height-normalized anthropometric central fat surrogate markers to predict cardiometabolic risk in the general and overweight-obese population. BMI-normalization impairs risk assessment unless plasma lipid concentrations are available and included in calculations.

1. Introduction

High body mass index (BMI) as observed in overweight and obese individuals (>25 kg/m^2) is commonly associated with insulin resistance and related cardiometabolic risk factors defining the metabolic syndrome (MetS: elevated blood glucose and triglycerides, low HDL-cholesterol and high systolic and diastolic blood pressure) [1–4]. Central visceral fat accumulation further enhances metabolic abnormalities but is not routinely

Abbreviation list: AUC, Area Under the Curve; BMI, Body Mass Index; BRI, Body Roundness Index; HOMA, Homeostatic Model Assessment; MetS, Metabolic Syndrome; Ob, Obese; Ow, Overweight; ROC, Receiver Operating Characteristic; VAI, Visceral Adiposity Index; WC, Waist Circumference; WtoH, Weight-to-Height Ratio.

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measurable in clinical practice due to invasiveness as well as technical and financial issues [5–9]. Surrogate anthropometric markers of central fat are therefore commonly used in addition to BMI for patient risk stratification, and waist circumference is recommended for this purpose by recent clinical guidelines [1,2]. Height- (Weight-to-Height Ratio– WtoH; Body Roundness Index – BRI) or BMI-normalized markers of central fat distribution without (A Body Shape Index – ABSI) or with (BMI-normalized Visceral Adiposity Index – VAI) inclusion of plasma lipid parameters [10] have been however recently proposed as potential more specific WC-based indicators of central fat accumulation. Clinical interest in ABSI has been also raised by its association and higher predictive value for all-cause mortality compared to other anthropometric markers including BMI [10,11]. Whether height- and BMI-normalized surrogate markers of central visceral fat predict cardiometabolic risk in the general population and particularly in high-risk overweight-obese individuals remains however largely undefined. The potential impact of combining anthropometric variables and plasma metabolic parameters in predictive marker equations also should be directly investigated.

In the current study we therefore assessed associations between WtoH, BRI, ABSI or VAI and insulin resistance or metabolic syndrome in a general population cohort from the North-East Italy Mo.Ma. epidemiological study [12,13]. Predictive accuracy was compared to that of WC or BMI as established reference markers both cross-sectionally and longitudinally in a subgroup of overweight-obese individuals undergoing 5-year follow-up.

2. Methods

2.1. Experimental protocol and study population

2.1.1. Basal

The study population was recruited in the setting of the Mo.Ma. study, a Friuli-Venezia Giulia Region-supported project aimed at investigating the prevalence of metabolic syndrome in the municipalities of MOntereale Valcellina and MAniago, Pordenone, Italy [12,13]. The study was approved by the Pordenone Hospital Ethics Committee and each subject gave written consent to participate after receiving detailed oral and written information on its aims and risks. Exclusion criteria for the current investigation were previous diagnosis or clinical or laboratory evidence of liver failure or disease, renal failure (plasma creatinine above 1.5 mg/dl), cancer, thyroid disease, history of alcohol abuse or self-reported daily alcohol intake above 50 g. Smoking status was also assessed and defined as current smoker, non-smoker or ex-smoker after quitting for more than one year. In all study population, smoking status did not affect metabolic parameters or their interactions with anthropometric parameters. Smoking was therefore not included in analyses (not shown).

For data and plasma sample collection, each participant was admitted to the outpatient General Medicine wards in Montereale Valcellina or Maniago in the morning under post-absorptive conditions after a 10-h overnight fast. A blood sample was collected for measurement of routine variables for diagnosis of metabolic syndrome, a detailed medical examination was performed, and medical history was collected. Blood pressure was measured on the right and left arms using a standard mercury sphygmomanometer. Waist circumference (WC) was measured on bare skin during mid-respiration at the natural indentation between the 10th rib and iliac crest to the nearest 0.5 cm. General characteristics of the whole Mo.Ma. population sample have been previously reported [11]. Metabolic syndrome was diagnosed according to ATP III criteria [14]. Presence of diabetes mellitus, hypertension or dyslipidemia was defined based on clinical history, medications or, respectively, by fasting plasma glucose $\geq$126 mg/dl, systolic or diastolic blood pressure $\geq$140 or 90 mmHg, plasma triglycerides (TG) $\geq$ 150 mg/dl or plasma HDL cholesterol < 40 mg/dl in males and 50 mg/dl in females.

2.1.2. Follow-up

The follow-up study was aimed at assessing predictive values of anthropometric parameters for the presence of metabolic syndrome at 5-year follow-up in a sample of overweight-obese individuals (BMI>25) undergoing basal observation for sex, age and BMI. The follow-up group was selected by randomly inviting 350 individuals from the whole basal overweight-obese cohort, based on a priori power analysis considerations as detailed in the statistical analysis section. 263 individuals responded positively and participated in this study. Representativeness of the subgroup was statistically tested a posteriori as described in the statistical analysis section.

2.2. Plasma metabolic profile and calculated parameters

Plasma glucose, triglycerides, total and high-density lipoprotein (HDL) cholesterol and insulin concentrations were measured using standard methods at the Clinical Analysis Laboratory of Pordenone Hospital, Italy. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BRI, ABSI and VAI were calculated as previously reported [10,15,16] using the following formulas: BRI = 364.2−365.6 * $\sqrt{}$(1-(((WC/2π)^2)/((height/2)^2))); ABSI = WC/((BMI^2/3)*(Height^1/2)); VAI_{males} = (WC/(1.88*BMI+39.68)) * (TG/1.03) * (1.31/HDL); $VAI_{females}$ = (WC/(1.89*BMI+36.58)) * (TG/0.81) * (1.52/HDL). Insulin sensitivity was calculated through the validated surrogate marker homeostasis model assessment (HOMA) index [17] using the following formula: HOMA = (FPG * FPI)/22.5, where FPG and FPI are fasting plasma glucose (mmol) and fasting plasma insulin (μU/ml), respectively.

2.3. Statistical analysis

Data distribution of continuous variables was assessed by Shapiro–Wilk test. Several parameters, including HOMA, did not present normal distribution, therefore associations between variables were at first investigated using Spearman correlation analysis and, where appropriate, log-transformed values were subsequently used in further analysis. Follow up sample size was chosen a priori considering a the possibility to detect a small effect size (f^2 = 0.05, α = 0.05) with good statistical power (π = 0.80) in multiple regression analysis with up to 5 predictors (G*Power software, v. 3.1.9.2, Universität Kiel, Kiel, Germany). This same sample size was also checked to be adequate to identify with good power (α = 0.05, π = 0.80) small-size area under the curve (AUC) differences (7% at AUC = 0.80 level) between surrogate markers in receiver operating characteristic (ROC) analysis [18]. Based on previous experience with the studied population, 40% more individuals were contacted in order to correct non participation. Representativeness of the overweight-obese follow-up sample was tested a posteriori for the recorded basal parameters by one-sample t-test against the whole overweight-obese group. Where appropriate Mann–Whitney u test was used. Percentage expressed data was checked by χ-square test. Factors showing association ($p < 0.05$)

with HOMA index, as well as clinically relevant potential confounders, were included in stepwise multiple linear regression models in order to assess their impact in the relationship between HOMA and BMI, WC, VAI and ABSI. Multiple linear regression analyses were validated by assessing the normality of residuals. Associations of the same parameters with metabolic syndrome were similarly tested using binary logistic multiple regression analysis. Correlations were compared using the z-test method according to Meng, Rosenthal and Rubin [19]. Quartile analyses were performed by ANOVA followed by post-hoc tests. Evaluation of differences in basal BMI, WC, VAI and ABSI between subjects who did or did not develop Metabolic Syndrome at follow-up was performed by Student's t test. ROC analysis was followed by AUC comparison [20] between investigated parameters. All multiple comparisons were corrected according to Bonferroni. Except where otherwise indicated, data are presented as mean ± standard deviation (SD). P values < 0.05 were considered statistically significant. Analyses were performed using the SPSS v.17 software (SPSS Inc., Chicago, IL).

3. Results

3.1. Basal

3.1.1. Anthropometric and metabolic parameters (Table 1)

Anthropometric and metabolic parameters in the whole study population, in the whole overweight-obese subgroup and in the overweight-obese subgroup undergoing 5-year follow-up evaluation are reported in Table 1. No statistically significant differences between the two overweight-obese groups were observed at baseline for any variable.

Table 1
Study population. Gender, age, body mass index (BMI), waist circumference (WC), waist to height ratio (WtoH), body roundness index (BRI), a body shape index (ABSI), visceral adiposity index (VAI), plasma triglycerides, total and HDL cholesterol (Chol), glucose and insulin, homeostasis model assessment of insulin resistance (HOMA-IR), systolic (SBP) and diastolic (DBP) blood pressure; prevalence of diabetes mellitus, hypertension, hyperlipidemia at baseline in the whole study cohort and in all and selected overweight − obese (Ow-Ob) individuals that subsequently underwent 5-year Follow-Up (F-Up) evaluation. No statistically significant differences were observed between Ow-Ob subjects in the general population cohort and the Ow-Ob subgroup undergoing follow-up evaluation. Data are presented as mean ± SD.

BASAL	All	Ow-Ob	Ow-Ob F-Up
n	1965	1140	263
Gender (M)	911 (46.4%)	635 (55.7%)	138 (52.5%)
Age (y)	48.5 ± 13.0	51.7 ± 11.7	52.6 ± 8.8
BMI (kg/m^2)	26.71 ± 5.16	29.89 ± 4.36	30.71 ± 4.08
WC (cm)	92.8 ± 13.6	100.5 ± 11.2	102.4 ± 10.0
WtoH	0.557 ± 0.082	0.601 ± 0.72	0.609 ± 0.063
BRI	4.62 ± 1.83	5.55 ± 1.74	5.78 ± 1.52
ABSI	0.808 ± 0.058	0.808 ± 0.050	0.812 ± 0.047
VAI	1.809 ± 1.534	2.260 ± 1.802	2.391 ± 2.185
Triglycerides (mg/dl)	125.0 ± 83.3	147.4 ± 94.0	153.7 ± 112.5
Total-Chol (mg/dl)	208.9 ± 41.7	212.9 ± 41.9	213.7 ± 39.7
HDL-Chol (mg/dl)	55.6 ± 14.6	52.5 ± 13.4	51.0 ± 12.8
Glucose (mg/dl)	95.7 ± 21.6	99.6 ± 24.7	100.2 ± 16.3
Insulin (μU/ml)	10.2 ± 7.5	12.8 ± 8.7	13.2 ± 8.4
HOMA-IR	2.50 ± 2.48	3.28 ± 3.01	3.40 ± 2.73
SBP (mmHg)	134.5 ± 18.5	139.5 ± 18.0	141.5 ± 18.4
DBP (mmHg)	80.7 ± 10.4	83.3 ± 10.0	84.5 ± 9.6
Diabetes (%)	8.4	13.5	14.8
Hypertension (%)	45.7	62.3	64.4
Dyslipidemia (%)	24.1	33.6	37.3
MetS (%)	25.3	39.6	43.0

3.1.2. Associations between HOMA or MetS diagnosis and anthropometric or biochemical variables (Table 2; Figs. 1 and 2; Supplementary Table 1)

In all subjects, HOMA and the presence of MetS were associated positively with all analyzed parameters; similar associations were observed in separate analyses for the overweight-obese population except for total cholesterol (Figs. 1 and 2; Supplementary Table 1). Associations between HOMA or MetS and height-normalized indexes WtoH and BRI or WC and BMI remained statistically significant after adjusting for age and gender (Model 1), HOMA, plasma triglycerides and mean arterial pressure (Model 2a) or diagnosis of diabetes, hyperlipidemia and hypertension (Model 2b) (Table 2). Associations between BMI-normalized ABSI and HOMA index were in contrast no longer statistically significant after adjustments (Table 2). In addition, in comparative analyses [19] the strength of associations with HOMA index was higher for height-normalized parameters, WC and BMI than for ABSI in both the whole-study and in the overweight-obese population (Fig. 1, Supplementary Table 1), thereby indicating lower accuracy for ABSI in identifying insulin resistance in these groups. At variance with ABSI, associations between HOMA and MetS and VAI remained statistically significant after multiple adjustments; in addition, except for the association between HOMA and VAI in the whole study cohort the strength of all associations between HOMA or MetS and VAI was comparable to or stronger than those observed for height-normalized parameters, WC or BMI (Table 2).

3.1.3. HOMA or MetS prevalence in BMI, WC, VAI and ABSI quartiles (Supplementary Figure 1)

In quartile analyses of the whole or overweight-obese gender- and age-adjusted database, WtoH and BRI quartiles showed corresponding step-wise increments in HOMA index and MetS prevalence both in the whole and in the overweight-obese population (Supplementary Figure 1). In contrast, and consistent with weaker linear associations, stepwise HOMA and MetS prevalence increments were not observed for BMI-adjusted ABSI quartiles. Also consistent with association analyses, HOMA index and MetS prevalence increased in stepwise fashion in increasing VAI quartiles (Supplementary Figure 1).

3.1.4. Lean subgroup analyses (Supplementary Tables 2, 3)

Similar although weaker associations compared to the whole cohort or the overweight-obese population were found in correlation analyses between HOMA or MetS and all markers in the Lean subgroup.

3.2. Follow-up

3.2.1. Associations between basal parameters and 5-year MetS (Table 2; Figs. 3 and 4; Supplementary Table 1)

Similar to basal BMI and WC, height-normalized WtoH and BRI were associated positively with 5-year HOMA and MetS in association (Supplementary Table 1) and ROC analyses (Fig. 3) in the Ow-Ob subgroup undergoing follow-up. In contrast, no statistically significant associations were observed between ABSI and either 5-year HOMA or MetS. At variance with ABSI, BMI-normalized VAI with inclusion of lipid parameters was also a positive predictor of 5-year HOMA or MetS and indeed it showed the greatest AUC in ROC analyses for MetS prediction (Fig. 3). Basal plasma triglycerides, plasma glucose, insulin and HOMA index as well as diagnosis of diabetes, hyperlipidemia and hypertension were all associated with 5-year HOMA and MetS, whereas negative associations were observed between 5-year variables and plasma HDL cholesterol (Supplementary Table 1). Height-normalized WtoH and BRI, WC,

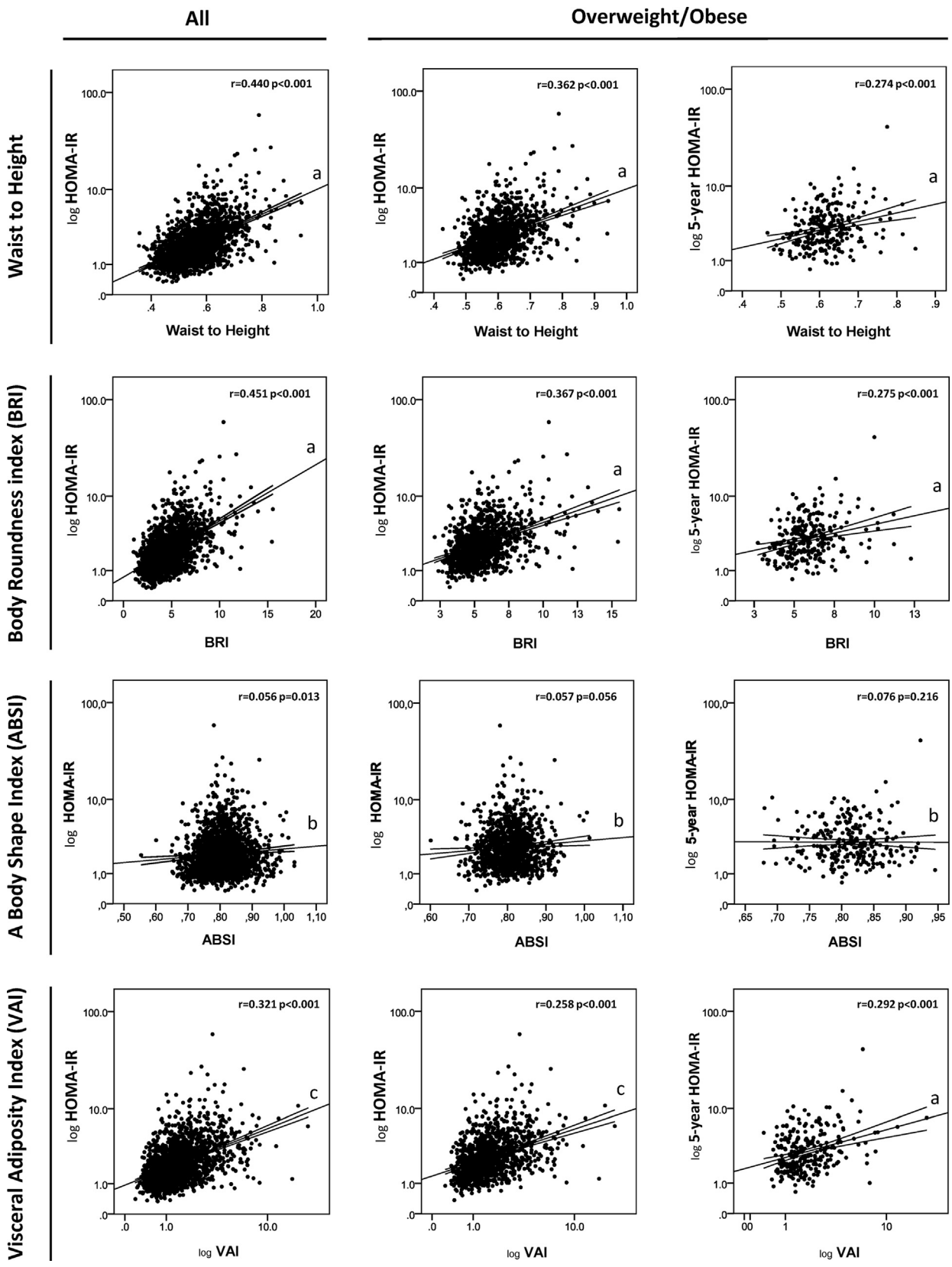


Fig. 1. Scatter plots of Waist to Height (WtoH), Body Roundness Index (BRI), A Body Shape Index (ABSI) and Visceral Adiposity Index (VAI) vs. basal HOMA-IR insulin resistance index in all subjects from the genaral population study cohort (n = 1945) and in overweight/obese individuals (n = 1140). The right column shows scatter plots for basal WtoH, BRI, ABSI and VAI vs. 5-year HOMA-IR in overweight/obese subjects with follow-up data (n = 263). Linear regression lines with confidence intervals, Pearson's correlation r and p values are provided for log-transformed HOMA-IR plots. Within each group, different letters next to regression lines indicate different ($p < 0.05$) strengths in parameter association with HOMA-IR, as assessed by Meng, Rosenthal and Rubin's z-test.

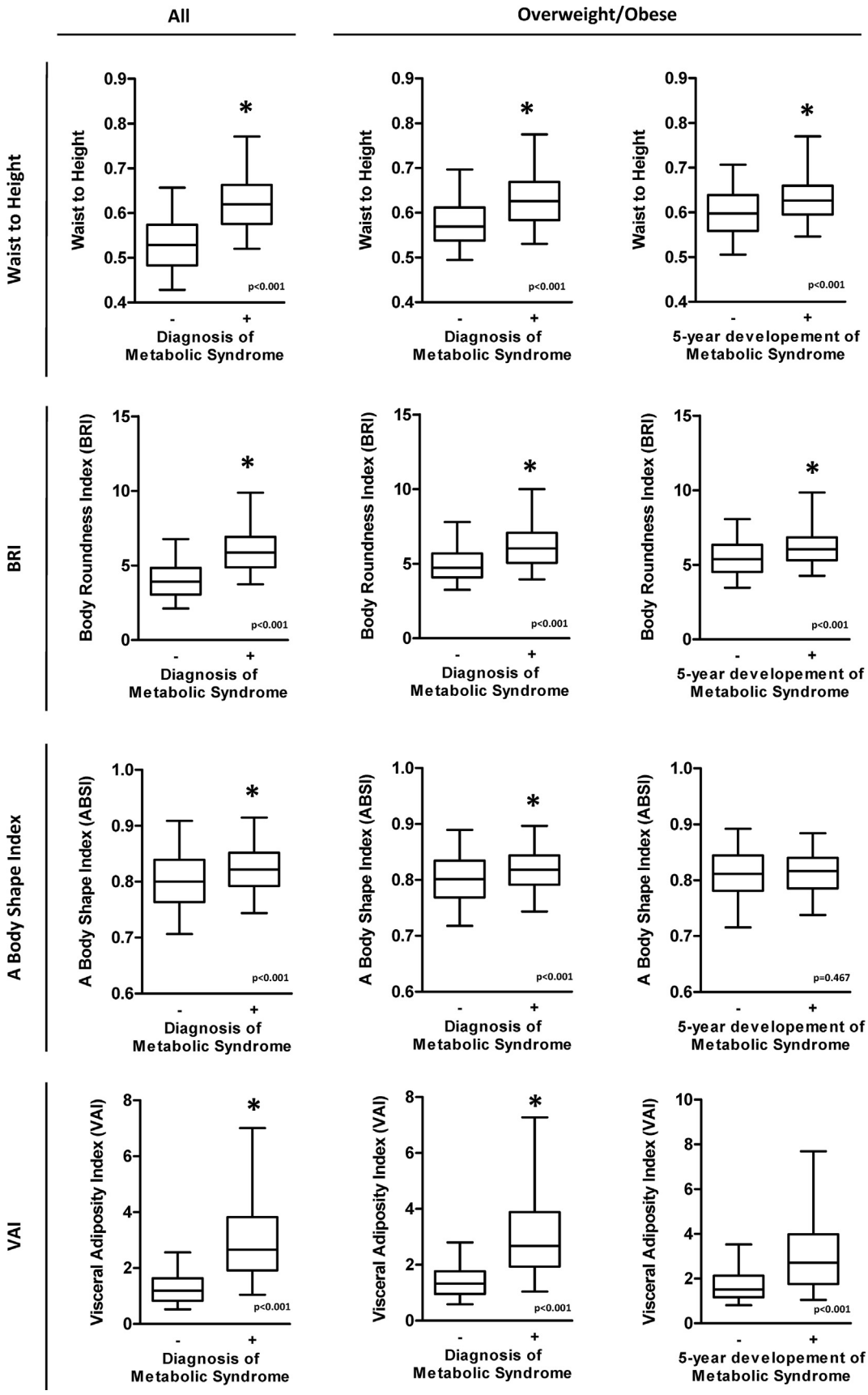


Fig. 2. Box plots of Waist to Height (WtoH), Body Roundness Index (BRI), A Body Shape Index (ABSI) and Visceral Adiposity Index (VAI) vs. Metabolic Syndrome status (MetS) in all subjects from the genaral population study cohort (n = 1945) and in overweight/obese individuals (n = 1140). The right column shows scatter plots for basal WtoH, BRI, ABSI and VAI vs. 5-year MetS in overweight/obese subjects with follow-up data (n = 263). Box indicates median, 25 and 75 percentiles, whiskers 5 and 95 percentiles; *p < 0.05 vs. subjects MetS-; actual p value is shown in the lower right corner of each graph.

Table 2

Multiple regression analyses. Multiple regression analyses between body mass index (BMI), waist circumference (WC), waist to height ratio (WtoH), body roundness index (BRI), a body shape index (ABSI) and visceral adiposity index (VAI) and HOMA-IR or presence of Metabolic Syndrome in the whole study population (n = 1945), in obese-overweight subjects at baseline level (n = 1140) and in obese-overweight individuals selected for follow-up evaluation (n = 263) vs. 5-year HOMA-IR or presence of Metabolic Syndrome in different statistical adjustment models. B: Coefficient, SE: Standard Error; t: t value; z: Wald test.

Basal	Model	All				Obese/Overweight				5-year Obese/Overweight			
		Basal HOMA-IR								5year HOMA-IR			
		B	SE	t	p	B	SE	t	p	B	SE	t	p
BMI	1	0.238	0.010	23.965	<0.001	0.305	0.019	16.495	<0.001	0.258	0.047	5.430	<0.001
	2a	0.223	0.010	21.563	<0.001	0.292	0.018	15.815	<0.001	0.246	0.048	5.115	<0.001
	2b	0.203	0.010	20.563	<0.001	0.261	0.018	14.781	<0.001	0.208	0.047	4.409	<0.001
WC	1	0.107	0.007	14.428	<0.001	0.086	0.004	21.353	<0.001	0.109	0.019	5.783	<0.001
	2a	0.102	0.007	13.836	<0.001	0.079	0.004	19.056	<0.001	0.103	0.019	5.521	<0.001
	2b	0.088	0.007	12.333	<0.001	0.070	0.004	17.522	<0.001	0.088	0.019	4.662	<0.001
WtoH	1	14.059	0.668	21.052	<0.001	17.817	1.246	14.297	<0.001	16.792	3.103	5.412	<0.001
	2a	12.742	0.684	18.616	<0.001	16.782	1.238	13.552	<0.001	15.665	3.096	5.060	<0.001
	2b	11.352	0.658	17.246	<0.001	14.565	1.190	12.240	<0.001	13.424	3.080	4.358	<0.001
BRI	1	0.645	0.030	21.826	<0.001	0.736	0.051	14.413	<0.001	0.703	0.129	5.467	<0.001
	2a	0.589	0.030	19.487	<0.001	0.694	0.051	13.699	<0.001	0.656	0.128	5.118	<0.001
	2b	0.524	0.029	17.996	<0.001	0.601	0.049	12.337	<0.001	0.564	0.128	4.423	<0.001
ABSI	1	1.105	0.976	1.132	0.258	2.272	1.862	1.220	0.223	4.843	4.303	1.125	0.261
	2a	0.995	0.939	1.059	0.290	2.198	1.815	1.211	0.226	5.168	4.245	1.217	0.225
	2b	0.002	0.889	0.002	0.998	0.483	1.710	0.282	0.778	3.491	4.106	0.850	0.396
VAI	1	0.548	0.039	14.018	<0.001	0.481	0.054	8.897	<0.001	0.479	0.100	4.795	<0.001
	2a	0.759	0.101	7.526	<0.001	0.652	0.146	4.479	<0.001	1.202	0.288	4.170	<0.001
	2b	0.335	0.048	7.003	<0.001	0.272	0.064	4.233	<0.001	0.331	0.118	2.798	0.006
		Basal Metabolic Syndrome								5-year Metabolic Syndrome			
		B	SE	z	p	B	SE	z	p	B	SE	z	p
BMI	1	0.234	0.014	267.663	<0.001	0.179	0.018	101.878	<0.001	0.176	0.038	21.832	<0.001
	2a	0.149	0.017	77.995	<0.001	0.116	0.021	31.730	<0.001	0.108	0.042	6.628	0.010
	2b	0.251	0.020	158.944	<0.001	0.204	0.024	71.809	<0.001	0.140	0.041	11.894	<0.001
WC	1	0.103	0.006	285.349	<0.001	0.078	0.007	122.576	<0.001	0.063	0.014	19.360	<0.001
	2a	0.124	0.009	182.626	<0.001	0.102	0.010	97.119	<0.001	0.043	0.016	7.027	0.008
	2b	0.079	0.007	116.198	<0.001	0.064	0.008	57.118	<0.001	0.048	0.016	9.444	0.002
WtoH	1	16.674	1.007	274.382	<0.001	12.464	1.173	112.889	<0.001	10.919	2.422	20.330	<0.001
	2a	11.914	1.169	103.906	<0.001	9.448	1.369	47.605	<0.001	7.635	2.661	8.232	0.004
	2b	18.881	1.444	170.879	<0.001	15.129	1.650	84.090	<0.001	8.933	2.672	11.173	0.001
BRI	1	0.713	0.044	260.270	<0.001	0.509	0.050	104.293	<0.001	0.435	0.101	18.660	<0.001
	2a	0.493	0.051	94.918	<0.001	0.375	0.057	43.042	<0.001	0.296	0.109	7.323	0.007
	2b	0.785	0.062	160.894	<0.001	0.599	0.069	76.199	<0.001	0.347	0.110	9.878	0.002
ABSI	1	4.417	0.993	19.774	<0.001	5.607	1.331	17.736	<0.001	1.532	2.706	0.320	0.571
	2a	6.220	1.258	24.451	<0.001	7.078	1.624	18.998	<0.001	3.053	3.114	0.961	0.327
	2b	6.459	1.411	20.971	<0.001	8.803	1.905	21.349	<0.001	0.917	3.091	0.088	0.767
VAI	1	1.419	0.080	312.462	<0.001	1.348	0.095	203.214	<0.001	0.892	0.154	33.590	<0.001
	2a	2.236	0.191	137.063	<0.001	2.273	0.228	99.029	<0.001	1.114	0.354	9.872	0.002
	2b	0.961	0.116	68.924	<0.001	0.789	0.129	37.288	<0.001	0.488	0.195	6.272	0.012

Data adjustments.
Model 1: Age, Gender.
Model 2a: Model 1 + HOMA (not for HOMA), MAP, Triglycerides.
Model 2b: Model 1 + Diabetes, Hypertension, Hyperlipidemia.

BMI and VAI remained however positively associated with 5-year HOMA and MetS after multiple adjustments (Table 2). Also in agreement with the above combined observations, patients without MetS at baseline evaluation who developed MetS after 5 years (n = 35) had higher basal WC, BMI, height-normalized parameters and VAI but superimposable ABSI compared to patients who remained without MetS (n = 115; Fig. 4).

3.2.2. Utilization of plasma lipid concentrations modulates cardiometabolic risk prediction by BMI-normalized surrogate markers (Fig. 3E–I)

ABSI and VAI showed profoundly different abilities in cardiometabolic risk prediction despite similar BMI-normalized, WC-based equation [10,15]. ABSI and VAI equations however differ due to inclusion of transformed plasma triglyceride and HDL-cholesterol concentrations in VAI but not ABSI calculation [10,15]. We therefore hypothesized that plasma triglycerides and HDL-cholesterol concentrations play a key role in preserving the ability of VAI to predict cardiometabolic risk prediction in overweight and obese individuals. In order to test this hypothesis, ROC analyses for 5-year MetS prediction by VAI and ABSI were calculated after exclusion of plasma lipid concentrations from VAI equation (VAI-) or after their addition to ABSI equation (ABSI+). In agreement with the hypothesis, VAI- no longer predicted 5-year MetS whereas ABSI + became its strongest predictor in ROC analyses (Fig. 3), with corresponding parallel changes in AUC. The current results strongly support the concepts that: 1) BMI-normalized surrogate markers of central fat accumulation per se are weak predictors of overweight- and obesity-associated cardiometabolic risk; 2) inclusion of plasma triglyceride and HDL-cholesterol strongly improves cardiometabolic risk prediction of BMI-normalized central fat surrogate markers.

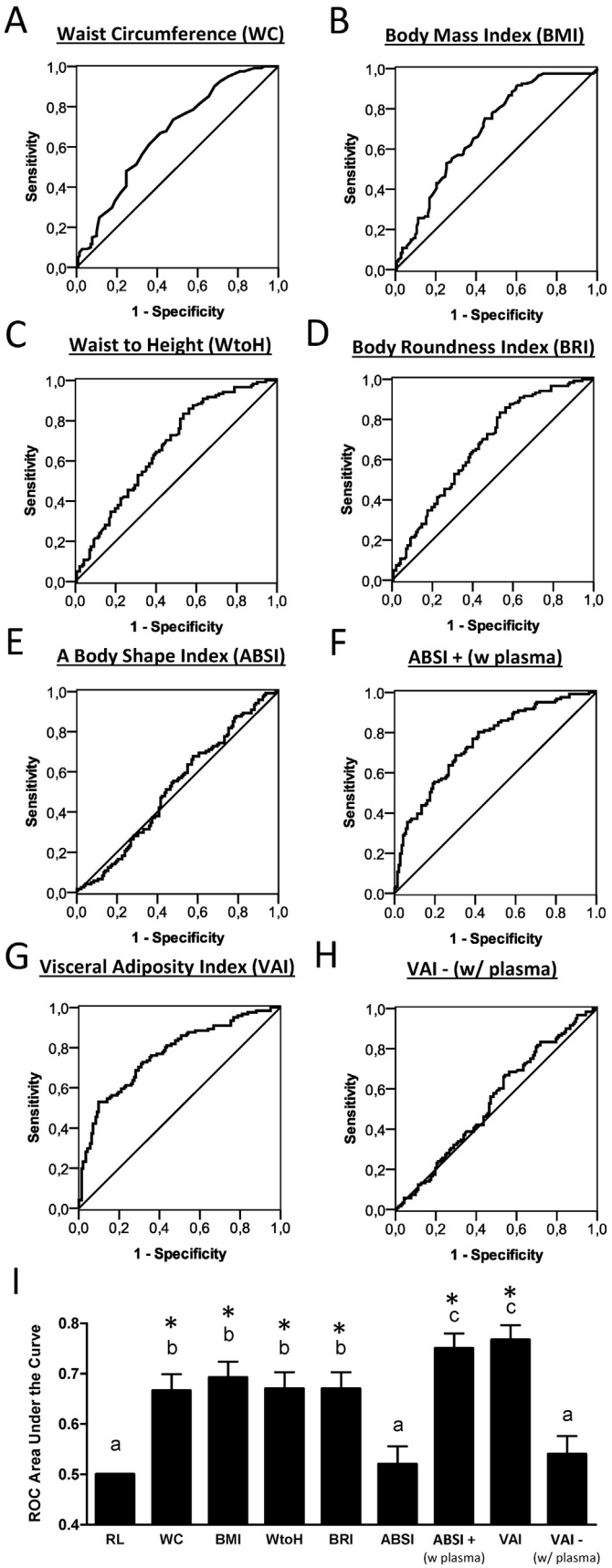


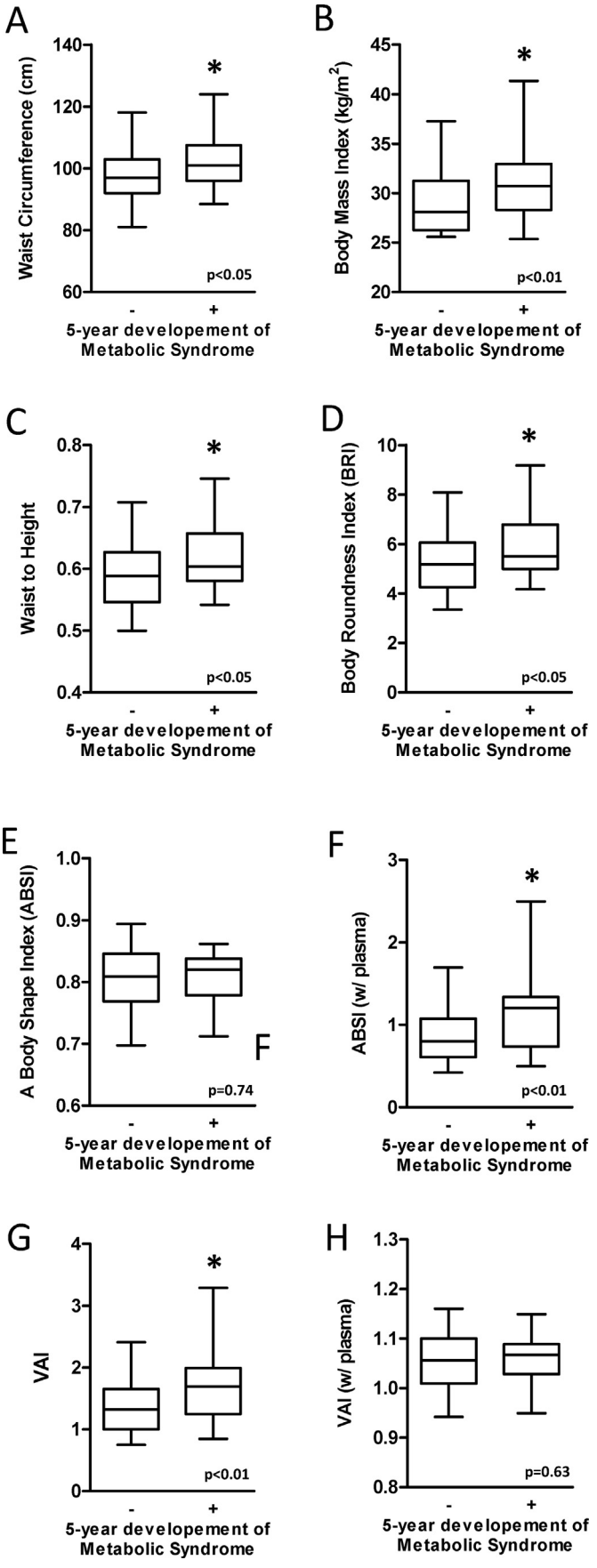
Fig. 3. Prediction for 5-years Metabolic Syndrome diagnosis of Waist Circumference (WC; A), Body Mass Index (BMI; B), Waist to Height Ratio (WtoH; C), Body Roundness Index (BRI; D), A Body Shape Index (ABSI; E), ABSI calculated without plasmatic data (w/plasma; F), Visceral Adiposity Index (VAI; G), VAI calculated without plasmatic data (w/plasma; H) in overweight/obese subjects with follow-up data (n = 263) as assessed by receiver operating characteristic curves (ROC), with Area Under the Curve comparative analysis (I).

4. Discussion

The current study investigated whether calculated surrogate markers of central body fat accumulation are superior to currently recommended waist circumference and BMI. Our findings demonstrate that 1) height-normalized WtoH and BRI effectively identify and predict metabolic complications in the general population and in high-risk overweight-obese individuals but they offer no further clinical advantage over waist circumference and BMI; 2) BMI-normalization per se results in less accurate or no ability to identify and predict metabolic complications unless plasma lipid concentrations are available and included in calculations.

Identifying individuals prone to develop metabolic diseases and metabolic syndrome in the general population and particularly in high-risk overweight and obese individuals is a clinical priority, due to sustained and ongoing major increments in overweight and obesity worldwide. While waist circumference is the currently recommended tool for patient risk stratification [1], adjustment for height or BMI has been recently proposed for potentially more accurate assessment of central fat accumulation independent of body shape and body mass. The ability of calculated markers to identify and predict overweight- and obesity-associated metabolic complications remains however incompletely defined, and it was therefore investigated in the current study in a general population cohort both cross-sectionally and following a 5-year follow up in a representative overweight-obese subgroup. The current results demonstrated that except for those combined with plasma lipids (VAI) none of the calculated, adjusted surrogate markers was superior to waist circumference in identifying and predicting insulin resistance and metabolic syndrome. Indeed BMI-normalization per se markedly impaired prediction of metabolic complications particularly in overweight and obese individuals. Interestingly and perhaps not surprisingly, inclusion of independent biomarkers of metabolic complications such as plasma triglycerides and HDL-cholesterol as designed for VAI calculation [15] resulted in preserved ability for risk identification in cross-sectional analyses and even enhanced ability to predict metabolic syndrome at follow-up. Based on this observation, plasma triglycerides and HDL-cholesterol should therefore be used whenever available for VAI calculation and more accurate risk assessment. Inability to predict complications after removal of its plasma lipid component conversely strongly indicates that the anthropometric component of VAI does not contribute to its ability to identify at-risk individuals. Overall, the current results strongly indicate that use of anthropometric adjusted surrogate markers of central fat per se should not be recommended over waist circumference for high-risk patient identification for aggressive risk management strategies in the general population and most importantly in overweight-obese individuals, unless they are strengthened by inclusion of additional plasma risk markers with particular regard to lipid profile.

The negative impact of BMI-normalization on cardiometabolic risk assessment could result at least in part from strong co-linearity between BMI and waist circumference [21–23], likely interfering to impair their mutual interaction with cardiometabolic risk factors particularly in the overweight and obese BMI range. Indirectly consistent with this concept, ABSI and waist circumference had comparable predictive values for metabolic abnormalities in lean



individuals who showed weakest associations between BMI and HOMA or metabolic syndrome prevalence. It should be pointed out that ABSI was intriguingly reported to be a good predictor of mortality in general population cohorts [10,11]. Whereas co-linearity between BMI, waist circumference and metabolic abnormalities [21–23] could at least in part account for weak accuracy of ABSI in cardiometabolic risk prediction, associations between BMI and mortality remain at least partly controversial. No increments in overall mortality have been indeed reported for large BMI increments from the lean to the obese range [24–26], with J-shaped increments only occurring for highest BMI values and severe obesity. Lack of co-linearity between BMI and risk of death could therefore allow for improved mortality prediction by ABSI compared to BMI or waist circumference per se. Despite the potential relevance of ABSI as a predictor of mortality, the current results clearly indicate that ABSI should not be recommended for clinical use in predicting cardiometabolic risk.

Also importantly, the study further confirmed a strong predictive ability for cardiometabolic risk by BMI per se. BMI was indeed superimposable to waist circumference in identifying and predicting the prevalence and risk of future insulin resistance and metabolic syndrome in the general population and in overweight-obese groups. This finding is in excellent agreement with recent epidemiological studies [1,22] and it strongly supports the concept that increments in both BMI and waist circumference in middle-age and high-BMI populations may largely and similarly reflect increments in fat tissue that largely occur at central body level.

To the best of our knowledge, our study is original in reporting comparisons among a large array of available markers of central body fat accumulation to predict insulin resistance and metabolic syndrome in a large general population cohort including longitudinal assessment over time. The current findings are generally consistent by previous reports in smaller groups with selected disease conditions and with less comprehensive, cross-sectional analyses [27,28]. Other studies reported variable levels of predictive ability without direct comparison with gold-standard markers waist circumference and BMI [29,30]. Finally, we wish to point out that the current results are potentially limited to the studied population, and they should not be directly generally applied to other groups, particularly with substantial differences in age, ethnic background and potentially disease conditions.

In conclusion, we demonstrated that calculated anthropometric surrogate markers of central body shape and fat accumulation per se are not superior to currently recommended waist circumference in identifying and predicting major components of cardiometabolic risk in the general population and in high-risk overweight-obese individuals. Height-normalized WtoH and BRI effectively identify and predict metabolic complications, but they offer no advantage over waist circumference and BMI. BMI normalization per se indeed results in loss of cardiometabolic predictive ability, that may be prevented by inclusion of plasma biochemical risk biomarkers. The current findings do not support replacement of WC with height- and body mass-normalized anthropometric central fat surrogate markers to predict cardiometabolic risk in the general and overweight-obese population, unless plasma lipid profile is available to allow for VAI calculation.

Fig. 4. Basal Waist Circumference (WC; A), Body Mass Index (BMI; B), Waist to Height Ratio (WtoH; C), Body Roundness Index (BRI; D), A Body Shape Index (ABSI; E), ABSI calculated without plasmatic data (w/plasma; F), Visceral Adiposity Index (VAI; G), VAI calculated without plasmatic data (w/plasma; H) in overweight/obese subjects with (n = 35) or without (n = 115) new diagnosis of Metabolic Syndrome (MetS) at 5 year follow-up recall. *p < 0.05 vs. subjects non developing MetS; actual p value is shown in the lower right corner of each graph.

Funding

This work was supported by Friuli-Venezia Giulia Region through direct funding (L.R. 14/2012 art.7, commi 65–67).

Statement of authorship

RB designed research; PV, AS, MI conducted research; GGC, AS analyzed data; AG, GS, GGC, MZ, GG discussed results RB, GGC wrote/revised the paper; RB had primary responsibility for final content and acts as guarantor for this article. All authors read and approved the final manuscript.

Conflicts of interest

The authors have no conflict of interest to disclose.

Acknowledgements

The authors would like to thank Dr. Renato Tozzoli and Dr. Paolo Doretto and the personnel of the Clinical Analysis laboratory at Pordenone Hospital for their excellent work in plasma sample analyses and Ms. Michela Del Mistro for excellent coordination of subject recruitment in Montereale Valcellina and Maniago. Dr. Lorenza Mamolo, Dr. Alice Marquis Alpago-Novello and Mr. Giovanni Cremasco, Dept of Medical, Surgical and Health Sciences, University of Trieste, are finally acknowledged for skilful collaboration in clinical examinations.

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