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FULL RESEARCH PAPER
Arterial hypertension

Insulin resistance bio-anthropometric markers predict hypertension control in individuals without diabetes

Matteo Landolfo [1,2], Francesco Spannella [1,2]*, Federico Giulietti[2], Alessandro Gezzi[1,2], Simone Biondini[1,2], Elisabetta Fausti[1,2], Sara Moriglia[1,2], Mirko Di Rosa [3], Luca Soraci [4], and Riccardo Sarzani[1,2]

[1]Clinical and Molecular Sciences Department, Politecnica delle Marche University, Via Tronto 10/a, 60020 Ancona, Italy; [2]Clinical Medicine and Geriatrics, IRCCS INRCA, Via della Montagnola 81, 60020 Ancona, Italy; [3]Unit of Geriatric Pharmacoepidemiology and Biostatistics, IRCCS INRCA, Via della Montagnola 81, 60020 Ancona, Italy; and [4]Unit of Geriatric Medicine, IRCCS INRCA, Contrata Muoio Piccolo, 87100 Cosenza, Italy

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Aims Insulin resistance (IR), often associated with visceral adiposity, contributes to the development of dyslipidaemia and hypertension through various mechanisms. IR bio-anthropometric indices, such as triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C), triglyceride–glucose index (TyGi), TyGi–body mass index (TyGi-BMI), TyGi–waist circumference (TyGi-WC), lipid accumulation product (LAP), visceral adiposity index (VAI), and metabolic score for insulin resistance (METS-IR), correlate with hypertension risk and poor blood pressure control when assessed via office blood pressure (OBP). However, their associations with 24 h ambulatory BP (ABP) and antihypertensive therapy remain unclear. This study examines the relationships between IR indices and ABP in outpatients without diabetes.

Methods and results This cross-sectional study included 1336 outpatients undergoing ABP monitoring. IR indices were calculated, and antihypertensive therapy was assessed by medication count and treatment intensity score (TIS). After log-transformation and centreing of the IR indices, logistic regression models analysed associations between IR and uncontrolled 24 h ABP. Following a likelihood ratio test, restricted cubic spline (RCS) analyses were performed to model the non-linear relationship between the IR indices and the odds of uncontrolled 24 h blood pressure (BP). The cohort (mean age, 54.9 years; 58.3% male; mean BMI, 27.4 kg/m^2) showed median values of TG/HDL-C 2.07, TyGi-BMI 234.9, TyGi-WC 832.8, LAP 41.4, VAI 71.3, and METS-IR 41. Uncontrolled ABP (64.2%) was more prevalent in younger males with higher IR indices. METS-IR and TyGi-BMI were independently associated with uncontrolled ABP.

Conclusion METS-IR and TyGi-BMI were associated with uncontrolled ABP, independently of treatment status, sex, and age. These indices, derived from widely available parameters, provide practical tools for identifying patients with an increased risk of hypertension in real-life clinical settings.

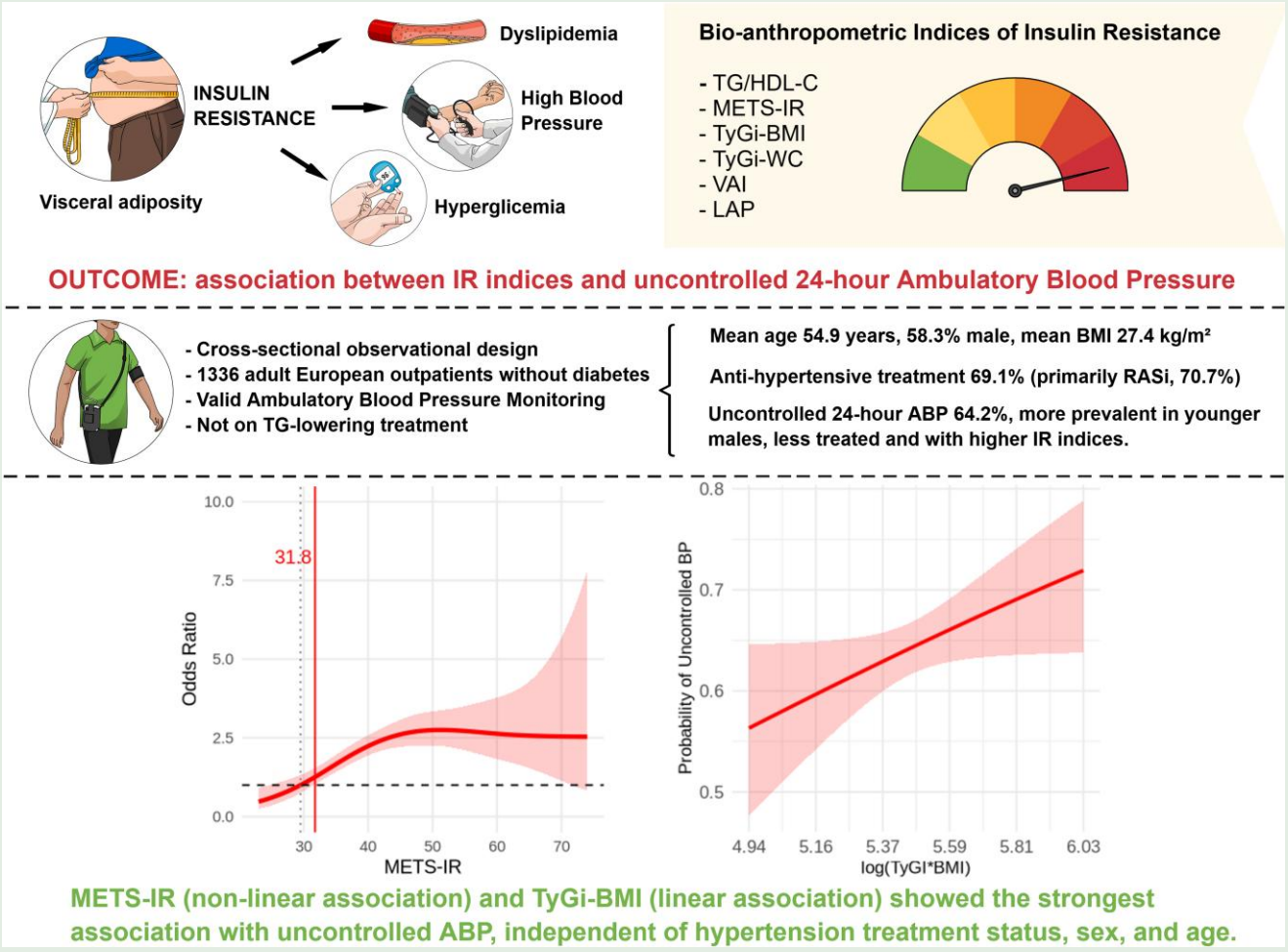
Lay summary This study investigated the relationship between insulin resistance (IR)—a condition commonly associated with abdominal obesity—and high blood pressure (BP) in European (Italian) patients without diabetes. Researchers specifically focused on how different measures of IR, based on available anthropometric and metabolic parameters, might be associated with uncontrolled 24 h BP, as measured using a device that monitors BP throughout the day and night.

- Higher IR levels were associated with uncontrolled BP despite treatment.
- Among IR measures, METS-IR and TyGi-BMI were the most reliable predictors of uncontrolled BP.

These findings are significant because the measures used to assess IR are simple and widely available. Healthcare providers could use them to identify patients at higher risk of poorly managed BP and tailor treatments accordingly.

* Corresponding author. Tel: +300718003289, Email: f.spannella@univpm.it

Graphical Abstract



Keywords Insulin resistance • Hypertension • Ambulatory blood pressure monitoring • TyGi-BMI • METS-IR

Introduction

Systemic essential arterial hypertension, affecting approximately one-third of the adult population, is the leading modifiable risk factor for cardiovascular disease (CVD) and all-cause morbidity and mortality worldwide.[1] Despite substantial efforts to reduce the global health and socio-economic burden associated with hypertension, achieving optimal control remains a distant target.[2] Insulin resistance (IR), a common metabolic condition often linked to visceral obesity, is characterized by altered glucose and lipid metabolism and compensatory hyperinsulinaemia. It is strongly associated with several cardiovascular risk factors, including hypertension.[3] IR contributes to the pathogenesis of hypertension through multiple mechanisms, including the hyperactivation of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS), which leads to increased renal sodium reabsorption and endothelial dysfunction.[4,5] Identifying IR as a potential contributor to hypertension and suboptimal blood pressure (BP) control could play a critical role in preventing CVD and slowing its progression. Such an approach underscores the necessity of redefining therapeutic strategies to address hypertension and cardiovascular risk in patients with IR. This includes incorporating innovative treatments, such as glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dual GLP-1/glucose-dependent insulinotropic peptide (GIP)-RA.[6,7] However, diagnosing IR in routine clinical practice poses challenges. The hyperinsulinaemic_euglycaemic clamp (HEC), the gold standard for IR assessment, is complex and impractical for widespread use. Alternative diagnostic tools, such as the homeostatic model assessment of insulin resistance (HOMA-IR), still require fasting insulin levels, which may limit their utility. In response, bio-anthropometric indices, derived from routine anthropometric measurements and standard laboratory parameters, have emerged as practical and reliable surrogates for IR. Notable examples include the metabolic score for insulin resistance (METS-IR), the triglyceride–glucose index (TyGi) and its derivatives incorporating body mass index (BMI) and waist circumference (WC) (TyGi-BMI and TyGi-WC, respectively), the triglyceride-to-high-density lipoprotein (HDL) cholesterol ratio (TG/HDL-C), the lipid accumulation product (LAP), and the visceral adiposity index (VAI). These indices have demonstrated high accuracy in assessing IR compared with HEC and HOMA-IR.[8–14] While several studies, primarily in Asian populations, have reported a positive association between specific bio-anthropometric indices of IR and hypertension,[15] evidence remains scarce regarding their utility in predicting BP control, particularly in 24 h ambulatory blood pressure (ABP) monitoring. Furthermore, data specific

to European populations are limited. This cross-sectional study aims to evaluate the association between emerging bio-anthropometric indices of IR and ABP control in a cohort of adults in Italy. By doing so, this study seeks to identify clinically helpful bio-anthropometric indices that provide valuable insights into the role of IR in hypertension management and its implications for cardiovascular risk reduction in a real-life clinical setting.

Methods

Study design, population, and aims

An observational cross-sectional single-centre study was conducted on a cohort of 1336 consecutive outpatients referred to our European Society of Hypertension (ESH) 'Excellence Centre' at Politecnica delle Marche University and Internal Medicine and Geriatrics Unit at Istituto Nazionale di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale di Riposo e Cura per Anziani (IRCCS INRCA), Ancona (Italy), from September 2023 to September 2024, for the evaluation and management of arterial hypertension, dyslipidaemia, and individual cardiovascular risk. The following inclusion criteria were considered: age ≥ 18 years and a valid ABP monitoring performed within the previous month. The exclusion criteria were overt diabetes mellitus (DM), TG > 400 mg/dL, HDL-C > 80 mg/dL, advanced renal disease [estimated glomerular filtration rate (eGFR) < 30 mL/min], secondary hypertension, obstructive sleep apnoea syndrome (OSAS), and TG-lowering drugs (i.e. fibrates). The endpoint of our study was to assess the presence, nature, and shape of the association between IR surrogate bio-anthropometric indices and uncontrolled 24 h BP, according to ABP, as outcomes. This investigation was conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments. The study was approved by the local institutional ethics committee (Comitato Etico IRCCS INRCA, Ancona).

Data collection and definitions

Data on demographics, anthropometrics, health-related behaviour, history of clinically relevant conditions, ongoing pharmacological treatments, resting vital parameters, and laboratory data were collected during or right after the office visit. Smoking habit was defined as current smoking or previous smoking of at least 100 cigarettes in a lifetime. BMI was calculated as weight in kilograms divided by height in metres squared and used as a continuous variable for analyses. For categorical presentation, standard cutoffs were applied to the unrounded continuous values (i.e. 25.0–29.9 kg/m^2 for overweight, ≥ 30.0 kg/m^2 for obesity).

WC was measured in the horizontal plane midway between the lowest ribs and the iliac crest. Hypercholesterolaemia and hypertension were defined by a personal history of taking lipid-lowering therapy (LLT) (statins and/or ezetimibe) and antihypertensive drugs. Approximately 30% were untreated hypertensive patients, defined according to the ESH ABPM criteria.[16] Chronic kidney disease (CKD) was described as an eGFR of <60 mL/min, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The laboratory included fasting serum glucose and a complete lipid profile, comprising total cholesterol (TC), HDL-C, triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), calculated using the Friedewald equation as modified by Martin–Hopkins. METS-IR was calculated using the following formula:[8]

$$\text{METS-IR} = \frac{\ln[(2 * \text{Fasting Glucose (mg/dL)}) + \text{Fasting TG (mg/dL)}] * \text{BMI (kg/mq)}}{\ln[\text{Fasting HDL-C (mg/dL)}]}$$

The TyGi was calculated as:[9]

$$\text{TyGi} = \ln\left(\frac{\text{Fasting TG (mg/dL)} * \text{Fasting Glucose (mg/dL)}}{2}\right)$$

After transforming TG from mg/dL to mmol/L, whenever WC was available ($n = 471$), the LAP was calculated by the following formulas:[17]

$$\text{Male LAP} = [\text{WC (cm)}\text{-}65] * \text{TG (mmol/L)}$$
$$\text{Female LAP} = [\text{WC (cm)}\text{-}58] * \text{TG (mmol/L)}$$

Also, after converting HDL-C from mg/dL to mmol/L, the VAI[18] was calculated as follows:

$$\text{Male VAI} = \left(\frac{\text{WC (cm)}}{39.68 + 1.88 * \text{BMI (kg/mq)}}\right) * \left(\frac{\text{TG (mmol/L)}}{1.03}\right) * \left(\frac{1.31}{\text{HDL-C (mmol/L)}}\right)$$

$$\text{Female VAI} = \left(\frac{\text{WC (cm)}}{39.58 + 1.89 * \text{BMI (kg/mq)}}\right) * \left(\frac{\text{TG (mmol/L)}}{0.81}\right) * \left(\frac{1.52}{\text{HDL-C (mmol/L)}}\right)$$

TyGi-BMI and TyGi-WC were the products of combining TyGi with BMI and WC, respectively. Additionally, the TG/HDL-C ratio was calculated from the basal fasting serum TG and HDL-C levels. The IR indices used in the analyses were selected based on their availability from routine anthropometric and laboratory data and their combination following good clinical practice within our outpatient facility. Additionally, the chosen indices have the most substantial evidence supporting their accuracy in diagnosing IR as an alternative to the HOMA index and the HEC.

For participants on BP-lowering therapy, the treatment intensity score (TIS) was used to calculate the average of different drug associations for antihypertensives, considering both the number of medications and their dosages. The recorded daily dose taken by patients was divided by the maximum recommended daily dose to obtain a proportional dose (intensity) for that medication. The maximum recommended daily doses established by the Italian National Agency for Drug Administration and Control (AIFA) were used for these calculations. Combined antihypertensive therapies were separated into components, and intensity was calculated separately for each compound. The sum of all the different values was recorded as the TIS.[19]

Ambulatory blood pressure measurement

A 24 h ABP monitoring was performed at baseline in each enrolled patient, using Spacelabs devices model 90227 (Spacelabs Healthcare, Snoqualmie, WA, USA) and TM-2430 ambulatory BP monitors (A&D Company, Tokyo, Japan) with appropriate cuff dimensions according to the arm circumference. Mean 24 h BP, daytime BP (defined as the BP values from 06:00 to 22:00 h), and night-time BP (defined as the BP values from 22:00 to 06:00 h) were considered. The definitions of 'day' and 'night' periods were based on the most common answers to a questionnaire in which patients were asked about their sleeping behaviour. The medical staff verified the correct positioning of the brachial cuff and its proper functioning, and minimum quality criteria for a satisfactory ABPM recording were based on the recommendations by Omboni *et al.*[20] Mean 24 h systolic/diastolic blood pressure (SBP/DBP) < 130/80 mmHg, mean daytime SBP/DBP < 135/85 mmHg, and mean night-time SBP/DBP < 120/70 mmHg defined acceptable BP control in hypertensive patients.

Statistical analysis

Normality of variables was assessed using the Shapiro–Wilk test and Q–Q plots. Levene's test evaluated the homogeneity of variances. When assumptions of normality or equal variances were violated, particularly in the presence of heteroscedasticity, Welch's *t*-test was used. Continuous variables were summarized as mean ± standard deviation (SD) or, when markedly skewed, as median and interquartile range (IQR). Categorical variables

were reported as frequencies and percentages. Group comparisons were performed using Student's *t*-test, Mann–Whitney U test, or χ^2 test, as appropriate. Variables such as METS-IR, TyGi-BMI, TyGi-WC, TG/HDL-C, LAP, and VAI, which involve non-parametric components and exhibit skewed distributions, were log-transformed using the natural logarithm (Logn) and mean-centred before inclusion in regression analyses.

Associations between IR indices and the binary outcome of uncontrolled ABP were assessed using multivariable logistic regression, reporting odds ratios (ORs) and 95% confidence intervals (CIs). Considering the outcome, potential clinical confounders were used as covariates in the regression models after excluding significant collinearity using the variance inflation factor (VIF). A VIF < 3 was considered acceptable, suggesting no critical multicollinearity. Three hierarchical models were specified: Model 1 adjusted for age (continuous) and sex (categorical), excluding sex from LAP and VAI due to sex-specific formulas, Model 2 additionally adjusted for antihypertensive therapy (categorical), and Model 3 further adjusted for TIS (continuous) and number of antihypertensive medications (continuous), in the subset of treated patients. A further analysis was conducted using the CLT as an interaction term.

To validate the findings, supervised machine learning was applied using a theory-driven covariate selection approach. LASSO regression with 10-fold cross-validation was used to optimize model performance. VIFs > 3 were excluded to mitigate multicollinearity. Details of LASSO model development and performance are provided in Supplementary material online, *Tables S1–S3*.

To explore potential non-linear effects of continuous predictors on outcome log-odds, we used likelihood ratio tests and the Box–Tidwell procedure. Non-significant results ($P > 0.05$) indicated no violation of the linearity assumption. Restricted cubic spline (RCS) regression was used to model non-linear associations between IR markers and uncontrolled 24 h BP. Models with three, five, and seven knots were compared using the Akaike information criterion (AIC), with the three-knot model ultimately selected for its balance between fit and parsimony.

All statistical analyses were conducted using IBM SPSS Statistics v23 (IBM Corp., Armonk, NY, USA) and R v4.3.6 (R Foundation for Statistical Computing, Vienna, Austria). R packages included *Caret* for model training and validation, *DescTools* for descriptive analyses, and *ModelMetrics* for evaluating performance metrics such as the Brier score.

Results

Characteristics of the overall study population and according to 24 h blood pressure control and treatment status

The general characteristics of the study population according to 24 h BP control are reported in *Table 1*. The study included a middle-aged sample, primarily men (58.3%), with a prevalence of patients with overweight and obesity of 47.4 and 25.7%, respectively. Ninety per cent of women were in menopause. The most prevalent cardiovascular comorbidities and risk factors were hypertension, followed by smoking and dyslipidaemia. The prevalence of CKD was 10%. Approximately 70% of patients were on antihypertensive treatment, with a median of two BP-lowering drugs taken and a median TIS of 1.11 (IQR 0.75–2). The most prevalent antihypertensive drugs taken were renin–angiotensin system inhibitors (RASi, 70.7%), followed by calcium channel blockers (CCB, 49.6%) and thiazide or thiazide-like diuretics (TZD, 36.9%). One-fourth of the participants were on LLT with a statin ± ezetimibe. The high prevalence of IR was corroborated by the high median scores of METS-IR, TyGi-BMI, TyGi-WC, TG/HDL-C, LAP, and VAI. According to ABP, 35.8% of the enrolled patients had a controlled 24 h BP profile. Those with uncontrolled 24 h BP were younger, primarily men with higher BMI, fewer cardiovascular comorbidities, and less treated for hypertension (lower TIS and number of antihypertensive medications). Regarding 24 h BP control, differences emerged in the median scores of the bio-anthropometric indices METS-IR and TyGi-BMI between groups, with slightly but significantly higher values in the hypertensive/uncontrolled 24 h BP group.

Risk of hypertension and uncontrolled 24 h blood pressure according to bio-anthropometric indices of IR

The distribution of the study outcome is reported in Supplementary material online, *Figure S1*. *Table 2* shows the results of the regression analysis for METS-IR and TyGi-BMI. In unadjusted analyses, higher METS-IR was significantly associated with uncontrolled 24 h BP, while TyGi-BMI showed a weaker, borderline association. Upon adjusting for covariates across successive models, METS-IR consistently remained a strong and statistically significant predictor of uncontrolled BP, with improved model discrimination and calibration metrics (higher AUCs and lower Brier scores). In contrast, TyGi-BMI lost significance in Models 1 and 2 but reached statistical significance in the fully adjusted Model 3. Across all models, older age was inversely associated, and male sex was positively associated with uncontrolled BP. Antihypertensive therapy and the number of antihypertensive medications were protective factors, while TIS showed no significant association. Overall, regarding the surrogate bio-anthropometric indices, METS-IR consistently showed strong and statistically significant associations with uncontrolled 24 h BP across all models. TyGi-BMI only achieved significance in the fully adjusted model. Other significant covariates included younger age, male sex, and lower use or number of antihypertensive medications.

In regression analyses including an interaction term for CLT, METS-IR consistently demonstrated the strongest and most stable association with uncontrolled 24 h BP across all models. In Model 3, METS-IR remained a significant predictor (OR = 3.28, 95% CI: 1.31–8.16, $P = 0.011$), with an AUC of 0.681 and a Brier score of 0.2144. The interaction between METS-IR and CLT was not statistically significant in any model ($P > 0.15$), suggesting the association between METS-IR and uncontrolled 24 h BP was largely independent of CLT status.

In contrast, the other IR-related indices (TyGi-BMI, TG/HDL-C, LAP, VAI, and TyGi-WC) failed to demonstrate consistent or significant associations across models. None of these indices reached significance in the fully adjusted Model 3 ($P > 0.05$), and their interaction terms with CLT were uniformly non-significant ($P > 0.19$). Notably, TyGi-BMI showed a borderline association in unadjusted analyses but lost significance after adjustment (Model 3 OR = 1.61, 95% CI: 0.63–4.15, $P = 0.323$). Similarly, TG/HDL-C, LAP, VAI, and TyGi-WC showed null or near-null associations.

Overall, these findings reinforce the superior predictive performance of METS-IR over other IR-related indices in identifying individuals with uncontrolled 24 h BP, even when accounting for LLT and other clinical covariates. Complete regression outputs are provided in Supplementary material online, *Tables S1* and *S2*.

Performance metrics for all models are reported in Supplementary material online, *Tables S3* and *S4*. Lasso regression with 10-fold cross-validation further underscored the superior classification performance of METS-IR compared with other metabolic indices. Across varying values of the regularization parameters α and λ, METS-IR consistently achieved the highest classification accuracy and Cohen's kappa, with peak performance at $\alpha = 1.00$ and $\lambda = 0.00184$ (accuracy = 0.947,

Table 1 Baseline characteristics of the study population according to 24 h BP control

	Overall (n = 1336)	24 h BP controlled (n = 478)	24 h BP uncontrolled (n = 858)	P-value[a]
Demographics and anthropometrics				
Age (years), median (IQR)	55 (45.8–65)	60 (49.2–69)	52.4(44–62)	$P < 0.001$
Sex (males, %)	58.3	49.6	63.2	$P < 0.001$
BMI (kg/m^2)	27 (24–30)	27 (24–31)	27 (24–30)	$P = 0.062$
Overweight (%)	47.4	43.8	49.4	$P = 0.052$
Obese (%)	25.7	23.3	30	$P = 0.007$
Cardiovascular comorbidities				
Smoking habit (%)	43.6	41.1	45	$P = 0.248$
Dyslipidaemia (%)	20.9	31	15.4	$P < 0.001$
CKD (eGFR < 60 mL/min/1.73m^2, %)	10	13.6	7.9	$P = 0.001$
Laboratory and bio-anthropometric indices of insulin resistance				
Glucose (mg/dL), median (IQR)	92 (85–100)	93.5 (86–102)	91 (85–99)	$P < 0.001$
Total cholesterol (mg/dL), mean ± SD	202.5 ± 38.7	201.2 ± 39.1	203.3 ± 38.4	$P = 0.342$
HDL-C (mg/dL), median (IQR)	51 (42–61)	51.5 (43–62)	51 (42–60)	$P = 0.198$
Triglycerides (mg/dL), median (IQR)	106 (79–147)	104.5 (79–146)	107.5 (78–148)	$P = 0.954$
LDL-C (mg/dL), mean ± SD	127 ± 34.3	125.3 ± 35.2	127.9 ± 33.8	$P = 0.181$
TG/HDL-C, median (IQR)	2.0 (1.4–3.3)	2.0 (1.4–3.2)	2.1 (1.4–3.3)	$P = 0.648$
TyGi-BMI, median (IQR)	234.9 (209.7–267.1)	229.5 (204–267)	236.5 (212.2–267.4)	$P = 0.032$
METS-IR, median (IQR)	41 (36–47)	39 (34–46)	42 (37–47)	$P < 0.001$
LAP (n = 471), median (IQR)	41.4 (27.6–65)	43.7 (29–66)	40.3 (27.1–64.7)	$P = 0.247$
VAI (n = 471), median (IQR)	71.3 (47–115.9)	74.3 (49–119.3)	70.8 (45.1–114.1)	$P = 0.478$
TyGi-WC (n = 471), median (IQR)	832.8 (758.9–927.8)	854.01 (752.3–930.1)	821.2 (760.1–920.1)	$P = 0.227$
Creatinine (mg/dL), median (IQR)	0.98 (0.8–1.1)	0.93 (0.8–1.1)	1 (0.8–1.1)	$P = 0.270$
eGFR (mL/min/1.73m^2), median (IQR)	79 (68–90)	77 (66–88)	80 (69–91)	$P < 0.001$
Cardiovascular pharmacological therapy				
Antihypertensive treatment (%)	69.1	75.9	65.3	$P < 0.001$
No. of antihypertensives, median (IQR)	2 (1–3)	2 (1–3)	2 (1–2)	$P < 0.001$
ACEI or ARB (%)	70.7	79.5	65	$P < 0.001$
Thiazide/thiazide-like diuretic (%)	36.9	44.6	31.8	$P < 0.001$
Dihydropyridine CCB (%)	49.6	48.8	50.1	$P = 0.693$
Alpha-blocker (%)	7.2	5.5	8.2	$P = 0.118$
Beta-blocker (%)	31.8	38	27.7	$P = 0.001$
Mineralocorticoid receptor antagonist (%)	3.7	4.7	3	$P = 0.196$
TIS for antihypertensives, median (IQR)	1.11 (0.75–2)	1.5 (1–2)	1 (0.5–1.86)	$P < 0.001$
Lipid-lowering therapy (%)	20.9	31	15.4	$P = 0.001$
Ambulatory blood pressure monitoring				
24 h SBP (mmHg), median (IQR)	130 (122–140)	120 (114–124)	137 (131–145)	$P < 0.001$
24 h DBP (mmHg), median (IQR)	80 (73–87)	72 (67–76)	85 (81–91)	$P < 0.001$
24 h BP control (%)	35.8	—	—	—
Daytime SBP (mmHg), median (IQR)	134 (125–144)	122 (117–128)	141 (134–148)	$P < 0.001$
Daytime DBP (mmHg), median (IQR)	83 (76–91)	75 (70–79)	88 (84–94)	$P < 0.001$
Daytime BP control (%)	41	—	—	—
Night-time SBP (mmHg), median (IQR)	122 (113–132)	111 (105–117)	128 (120–138)	$P < 0.001$
Night-time DBP (mmHg), median (IQR)	72 (65–80)	65 (59–69)	77 (71.5–83)	$P < 0.001$
Night-time BP control (%)	54.1	—	—	—

BP, blood pressure; BMI, body mass index; T2DM, Type 2 diabetes mellitus; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TG/HDL-C, triglyceride–HDL-C ratio; TyGi, triglyceride–glucose index; METS-IR, metabolic score for insulin resistance; LAP, lipid accumulation product; VAI, visceral adiposity index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; TIS, therapy intensity score; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a]P-value is for comparison between normotensive/24 h blood pressure controlled and hypertensive/24 h blood pressure uncontrolled. Note: Univariate P-values are presented solely to indicate differences between groups. These values do not imply causal or predictive associations with the outcome.

$\kappa = 0.884$). In contrast, TyGi-BMI yielded moderate performance (maximum accuracy = 0.847, $\kappa = 0.663$). At the same time, TG/HDL-C, LAP, VAI, and TyGi-WC all showed substantially lower accuracies (range, 0.639–0.688) and weak agreement ($\kappa < 0.21$ across all parameter settings).

Variable importance analysis from the final Lasso models (see Supplementary material online, *Table S4*) confirmed that METS-IR and TyGi-BMI were the most influential predictors (standardized importance = 100), whereas the traditional IR surrogates (TG/HDL-C, LAP, VAI, TyGi-WC) either showed zero or negligible influence in the models. In contrast, CLT, male sex, and the number of antihypertensive medications were consistently significant across models and emerged as the most critical risk factors in models that included weaker-performing indices. Notably, BMI was excluded due to multicollinearity (VIF > 3).

These findings reaffirm the robustness of METS-IR in predicting uncontrolled BP, both in conventional regression and in penalized machine learning models, and highlight its superior signal-to-noise ratio compared with other IR-related metrics.

The results of the likelihood ratio tests suggested a non-linear association between METS-IR and the odds of uncontrolled 24 h BP. The RCS model consistently outperforms the linear model in describing the relationship between METS-IR and the outcome, which appears to be non-linear across all models, with the most robust evidence for non-linearity in the unadjusted model and the model adjusted for age, sex, and treatment (Model 2). The shape of the association of METS-IR with the selected outcome, regardless of the adjustments, suggests that the association between METS-IR and uncontrolled 24 h BP is attenuated when adjusting for antihypertensive use (Model 2). However, after fully adjusting for additional covariates (Model 3), the association becomes more evident, particularly at higher METS-IR values. This suggests that factors such as TIS and the number of antihypertensive medications may significantly influence the relationship between METS-IR and uncontrolled 24 h BP. Conversely, the likelihood ratio tests for TyGi-BMI showed $P > 0.05$ for all models, indicating that the relationship between TyGi-BMI and the risk of hypertension and uncontrolled 24 h BP can be adequately described using a linear relationship. Consequently, after the Logn transformation of TyGi-BMI, the simpler linear models provided a significantly better fit than the more complex RCS. *Figure 1* illustrates the relationship between METS-IR and Logn TyGi-BMI and the risk of the outcome.

Discussion

The findings of our study address a debate regarding the association between bio-anthropometric indices of IR and arterial hypertension. Evidence linking these indices to hypertension and BP control remains limited, particularly for treated patients in European populations. Most existing data are derived from clinical studies on Asian or American cohorts. Furthermore, studies evaluating this relationship frequently rely on office BP measurements, which have greater variability, often without specifying the methods or devices used for assessment, and questionable diagnostic cut-offs are employed. This approach limits the reliability of hypertension diagnosis and BP control assessment, especially in patients undergoing anti-hypertensive treatment. The latest 2023 European Society of Hypertension (ESH) guidelines, as well as previous ones, emphasize the role of ABPM as the most reliable tool for diagnosing hypertension and assessing BP control, whether during lifestyle interventions or pharmacological treatment.[21]

Among the bio-anthropometric surrogate indices of IR evaluated in our study, only METS-IR and TyGi-BMI demonstrated an independent association with a higher risk of uncontrolled 24 h BP in the overall sample of real-life hypertensive patients. This association remained consistent across adjustments for Model 1 (age and sex), Model 2 (antihypertensive treatment), and Model 3 (number of antihypertensive medications and TIS). In contrast, other surrogate indices, including TG/HDL-C, LAP, VAI, and TyGi-WC, underperformed in predicting uncontrolled 24 h BP in real-life patients. Interestingly, the association between METS-IR and the outcome risk was non-linear, exhibiting a plateau effect and wider CIs at higher METS-IR values. On the other hand, TyGi-BMI displayed a linear association with the risk of uncontrolled 24 h BP. IR has been implicated in the elevation of BP through various pathophysiological mechanisms. Notably, its contribution in attenuating arterial responsiveness to vasodilatory stimuli has been extensively demonstrated across several anatomical regions, with a particular emphasis on skeletal muscle. This phenomenon is predominantly attributed to the dysregulation of the equilibrium between vasodilatory and vasoconstrictive mechanisms mediated by nitric oxide (NO) at the endothelial level. Consequently, endothelial dysfunction induced by IR has been recognized as a fundamental peripheral alteration contributing to the elevation of arterial BP.[22] Despite a substantial body of evidence derived from preclinical and clinical investigations demonstrating the strong relationship between IR and arterial stiffness (directly/invasively and indirectly/non-invasively assessed),[23,24] the extent to which this specific mechanism exhibits a 'plateau' effect—resulting in a dissociation between the severity of IR and the degree of hypertension or its suboptimal control—remains uncertain. Furthermore, the METS-IR, along with all the other indices, is derived from the combination of multiple individual variables, which may be subject to influences from numerous factors, according to the hypothesis that each index can reflect peculiar pathophysiological alterations. All the bio-anthropometric indices of IR considered in this study are derived from anthropometric and metabolic parameters typically altered in patients with IR. Compared with other IR scores, the superior performance of METS-IR and TyGi-BMI in predicting uncontrolled 24 h BP may be attributed to their more complex and comprehensive formulas. These formulas incorporate key phenotypical and pathophysiological features of IR that are particularly detrimental to BP regulation, such as BMI and basal glucose levels. Also, METS-IR incorporates HDL-C. HDL-C may play a crucial role in BP regulation beyond its traditional anti-atherogenic functions, as it promotes endothelial health through vasorelaxation mechanisms, including NO production, which helps maintain vascular tone. Lower HDL-C levels, a common marker of IR, reflect impaired lipid metabolism and diminished vascular protection, thereby exacerbating vascular stiffness and contributing to elevated BP.[25,26] The integration of HDL-C into metrics like the METS-IR underscores its relevance in metabolic and cardiovascular health, as observational and experimental studies consistently link reduced HDL-C concentrations with higher BP and a greater prevalence of hypertension. Indeed, under non-controlled experimental conditions and in the presence of unidentified confounding variables, it remains challenging to determine whether the observed non-linear relationship between the METS-IR and the risk of uncontrolled ambulatory BP is attributable to a threshold effect of IR. Our findings align with those of Chen *et al.*[27], who analysed the association of four bio-anthropometric indices of IR (TyGi, TyGi-BMI, TG/HDL-C, and METS-IR) with hypertension prevalence. Their study demonstrated that TyGi-BMI and METS-IR were independent risk factors for hypertension, with TyGi-BMI being slightly more accurate in predicting the outcome.

Table 2 Odds ratios and areas under the curve for uncontrolled 24 h blood pressure by METS-IR and TyGi-BMI in the overall population[a]

	Beta	SE	*P*-value	OR	95% CI lower	95% CI upper	AUC	Brier score
Unadjusted, *n* = 1336 (100%)/1336								
METS-IR	1.497	0.305	<0.001	4.47	2.46	8.124	0.581	0.2252
Constant	0.597	0.058	<0.001	1.816	1.622	2.034		
TyGi-BMI	0.629	0.321	0.05	1.875	1.0	3.516	0.535	0.2291
Constant	0.587	0.057	<0.001	1.798	1.608	2.012		
Model 1, *n* = 1336 (100%)/1336								
METS-IR	1.118	0.322	0.001	3.058	1.628	5.746	0.646	0.2165
Age	−0.027	0.004	<0.001	0.974	0.965	0.982		
Sex	0.32	0.123	0.009	1.378	1.082	1.754		
Constant	1.906	0.276	<0.001	6.724	3912	11.557		
TyGi-BMI	0.363	0.333	0.276	1.437	0.749	2.758	0.636	0.2186
Age	0.407	0.121	0.001	1.502	1.186	1.902		
Sex	−0.027	0.004	<0.001	0.973	0.964	0.981		
Constant	1.887	0.275	<0.001	6.6	3.847	11.325		
Model 2, *n* = 1336 (100%)/1336								
METS-IR	1.24	0.325	<0.001	3.455	1.827	6.535	0.653	0.2150
Age	−0.023	0.005	<0.001	0.977	0.968	0.986		
Sex	0.325	0.124	0.009	1.384	1.087	1.764		
Antihypertensive	−0.391	0.138	0.005	0.676	0.516	0.886		
Constant	1.976	0.28	<0.001	7.214	4167	12.486		
TyGi-BMI	0.483	0.336	0.151	1.62	0.838	3.132	0.643	0.2174
Age	−0.024	0.005	<0.001	0.976	0.967	0.985		
Sex	0.414	0.121	0.001	1.514	1.194	1.919		
Antihypertensive	−0.348	0.137	0.011	0.706	0.539	0.924		
Constant	1.953	0.279	<0.001	7.047	4.080	12.171		
Model 3, *n* = 916 (68.6%)/1336								
METS-IR	1.607	0.395	<0.001	4.989	2.302	10.811	0.680	0.2172
Age	−0.022	0.006	<0.001	0.978	0.967	0.99		
Sex	0.396	0.148	0.008	1.486	1.111	1.986		
TIS	0.05	0.153	0.741	1.052	0.78	1.419		
No. of antihypertensive	−0.346	0.133	0.009	0.707	0.545	0.919		
Constant	2.129	0.379	<0.001	8.406	4.000	17.668		
TyGi-BMI	0.857	0.406	0.035	2.356	1.064	5.219	0.670	0.2204
Age	−0.024	0.006	<0.001	0.976	0.965	0.988		
Sex	0.493	0.145	0.001	1.637	1.232	2.175		
TIS	0.051	0.151	0.737	1.052	0.782	1.416		
No. of antihypertensive	−0.325	0.132	0.014	0.723	0.558	0.937		
Constant	2.136	0.377	<0.001	8.468	4.047	17.716		

Model 1: adjusted for age and sex. Model 2: further adjusted for antihypertensive therapy. Model 3: further adjusted for TIS and number of antihypertensive medications.
AUC, area under the curve; METS-IR, metabolic score for insulin resistance; TyGi-BMI, triglyceride–glucose index body mass index.
[a]IR indices were log-transformed and centred before entering the regression analysis.

Similarly, cross-sectional studies in Asian populations have shown that TyGi-BMI exhibited the strongest association with hypertension.[14,28] In the only prospective investigation to date, individuals in the highest TyGi-BMI quartile had more than twice the risk of incident hypertension after full adjustment compared with those in the lowest quartile.[29] However, in contrast to our results, a previous cross-sectional study found that all tested bio-anthropometric indices of IR (TG/HDL-C, VAI, LAP, TyGi-BMI, and TyGi-WC) and their components were independently associated with hypertension, with no clear superiority among them. Interestingly, models that included only BMI and WC demonstrated predictive abilities comparable to most of the bio-anthropometric indices of IR.[30]

Our findings confirmed the independent association of higher quartiles of METS-IR and TyGi-BMI with uncontrolled 24 h BP across all models. Regression analysis further demonstrated that the number of antihypertensive medications, rather than the TIS, was independently associated with uncontrolled 24 h BP. This reinforces the concept that optimal BP control is generally more achievable through a multidrug, patient-centred, and pathophysiology-oriented approach, ideally using single-pill antihypertensive combinations, particularly in the

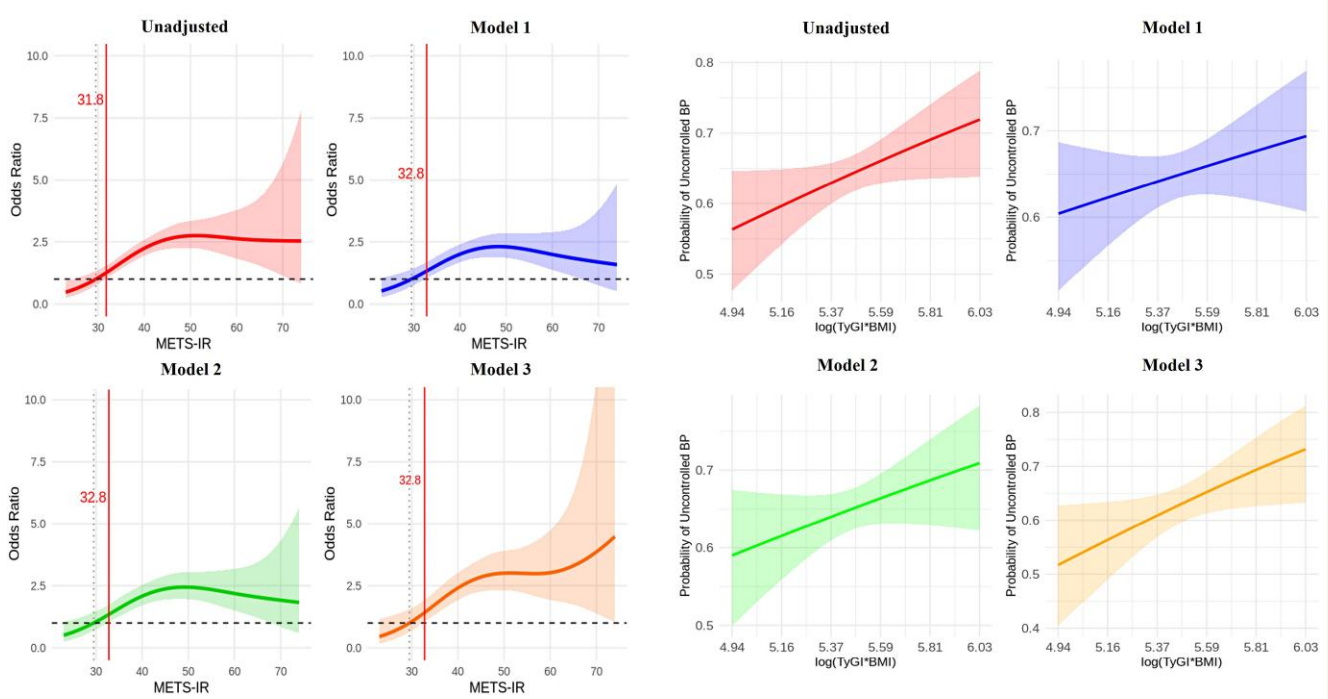


Figure 1 Restricted cubic splines showing the association of the METS-IR and the Logn TyGi-BMI with uncontrolled 24 h blood pressure in the unadjusted and adjusted models in the overall population. In the figure, the non-linear association of METS-IR with the outcome (left) and the linear association of Logn TyGi-BMI with the outcome (right) are shown.

context of complex and comorbid patients.[31,32] Our study was based on a cohort of Italian Caucasian adult outpatients referred for hypertension and cardiovascular risk evaluation and management. The overall population and its subgroups were primarily composed of middle-aged males with a high prevalence of overweight, cardiovascular comorbidities, and pharmacological therapies. Notably, two-thirds of the sample were already on antihypertensive treatment. Despite a relatively high TIS and multiple antihypertensive medications, 24 h BP control was achieved in only about two-thirds of patients, as demonstrated by ABPM. Consistent with the guidelines, the use of first-line antihypertensive drugs with the most robust indications for overweight/obese patients, such as RASi, TZD, and beta-blockers, was associated with improved 24 h BP control. Regarding age and sex, our analysis revealed that both are independently associated with the outcome, without compromising the performance of METS-IR or TyGi-BMI. In a previous trial involving older patients (>65 years), TyGi-BMI and METS-IR demonstrated the highest odds ratios (ORs) for hypertension, even after full adjustment (TyGi-BMI, OR 3.56, 95% CI: 2.70–4.70; METS-IR, OR 3.22, 95% CI: 2.45–4.24).[33] Similarly, another trial confirmed that TyGi-BMI was independently associated with incident hypertension in elderly patients.[29] While IR has been linked to hypertension in both sexes, evidence suggests that this relationship may vary due to differences in hormonal profiles, body fat distribution, and other physiological factors. Some studies propose that women may have a more pronounced risk of IR-related hypertension.[34] For instance, in a large Hispanic/Latino cohort not taking antihypertensive medications, IR (measured by HOMA-IR) showed a stronger association with systolic and diastolic BP in women compared with men.[35] Adiposity indices [e.g. BMI and waist-to-height ratio (WHtR)] were stronger predictors of hypertension in females than in males in a Chinese cohort.[36] One pathophysiological explanation could be the more significant impact of visceral adipose tissue on RAAS activity in women. Plasma aldosterone concentrations in obese premenopausal women correlated directly with visceral adiposity and BP but inversely with insulin sensitivity, associations not observed in men.[37] Similarly, authors reported higher hypertension risks in females within the highest quartile of IR surrogate indices.[29,30] However, our study revealed a more substantial and independent association between increasing values of METS-IR and TyGi-BMI with uncontrolled 24 h BP in the male subgroup. This finding contrasts with the hypothesis of a greater IR-related hypertension risk in women. It is important to note that evidence on sex differences remains inconsistent. While some studies did not detect sex-specific differences in the relationship between IR and hypertension,[38–41] others faced limitations, such as population-related biases or small subgroup sample sizes.[15]

Study strengths and limits

The present study possesses several distinctive strengths that enhance its scientific rigour and clinical relevance. First, the study cohort comprised an extensive and diverse European population, thereby improving the generalizability of the findings across various demographic contexts. Unlike investigations that rely solely on registries, our study utilized real-life clinical data derived from routine healthcare practices, providing valuable insights into everyday medical settings. Additionally, we conducted a comprehensive comparison of several validated surrogate indices of IR, thereby providing a robust evaluation of their relative utility in clinical practice. Importantly, our assessment extended beyond the mere diagnosis of hypertension to include the evaluation of BP control among patients already undergoing antihypertensive treatment,

thus addressing significant clinical outcomes. To ensure the accuracy and reliability of diagnostic outcomes, we employed rigorous and validated methods for hypertension diagnosis and BP control assessment, specifically through ABPM. Moreover, we accounted for the treatment burden by incorporating data from patients receiving antihypertensive pharmacological therapy and quantitatively characterizing this burden using the TIS alongside the number of medications, thereby providing an understanding of the therapeutic landscape. We acknowledge that the observational and cross-sectional design of our study presents several limitations. As a result, some critical information regarding known confounders, particularly therapeutic adherence to lifestyle modifications and antihypertensive medications, is unavailable. In this context, another limitation is that smoking status was determined through self-report, without biochemical verification such as cotinine levels. This may lead to misclassification, especially if participants underreport their smoking behaviour. Such misclassification could potentially attenuate the observed associations. However, considering that our data originate from a 'real-life' clinical setting, such information is typically obtained through self-reported questionnaires or surveys, which, even when available, are often imprecise. Moreover, accurately quantifying daily salt intake would require 24 h urine collection, which is not a standard clinical practice due to its complexity and time-consuming nature. Ensuring complete urine collection over 24 h poses significant challenges, including underestimation of actual sodium intake by approximately 10–15% (attributable to electrolyte losses through the skin and lungs) and interindividual variability in sodium excretion, which is further influenced by concurrent antihypertensive treatments. Further research with a longitudinal, controlled design is warranted to better understand the role of bio-anthropometric indices of IR in the comprehensive evaluation of hypertensive patients. These studies should validate these results in other European populations, address unaccounted confounders, and provide a clearer understanding of the causal implications of IR in the management of hypertension and BP control.

Conclusions

IR and hyperinsulinaemia are still undervalued as independent risk factors despite their increasing prevalence and well-documented role in the development of T2DM, hypertension, and CVD, thus remaining inadequately screened and targeted in the general population.[42] Readily available bio-anthropometric indices of IR, such as TG/HDL-C, TyGi, TyGi-BMI, TyGi-WC, LAP, VAI, and METS-IR, might help overcome this inertia. These indices combine routine blood tests with anthropometric measures, thereby bypassing the costs and complexity associated with hyperinsulinaemic-euglycaemic clamps (HEC) or HOMA-IR calculations based on basal serum insulin levels. Substantial evidence supports the clinical utility of bio-anthropometric indices of IR in predicting hypertension and uncontrolled BP, particularly when office BP cut-offs are used. Our study, using ABPM and its respective cut-offs, found limited utility for most indices, except for METS-IR and TyGi-BMI, which performed exceptionally well in men and older patients, making them the preferred tools for assessing IR in our real-life clinical context. These two IR bio-anthropometric indices, based on low-cost and generally available anthropometric and metabolic parameters, can identify real-life overweight or obese patients with an adipocentric, dysmetabolic higher risk of hypertension and uncontrolled 24 h BP.

Further studies are needed to explore alternative bio-anthropometric indices, particularly those that account for gender and age differences in hypertension risk. This would facilitate personalized cardiometabolic risk assessment and more targeted therapeutic approaches. While finalizing this manuscript, a relevant study highlighted a U-shaped association between TyGi-BMI and all-cause mortality.[43] Both low and high levels of TyGi-BMI were associated with reduced life expectancy. Unfortunately, this analysis focused solely on glucose- and TG-based indices. Given that hypertension is a critical risk factor for mortality, further studies evaluating a broader range of bio-anthropometric indices, including their relationship with hypertension, are warranted to understand their real-world clinical relevance.[44]

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contribution

R.S., M.L.: conceptualization, data curation, investigation, methodology, formal analysis, writing original draft. A.G., S.M., E.F., S.B.: data acquisition and curation. R.S., F.S., F.G.: resources, supervision, validation, project administration. M.D.R., L.S.: statistical analysis. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

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Ethical approval

All patients gave their written informed consent to participate in the present study. Clinical investigations have been conducted in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments. This observational study was approved by the local institutional ethics committee (Comitato Etico IRCCS INRCA).

Conflict of interest: none declared.

Data availability

The data supporting this study's findings are available from the corresponding author (F.S.) upon reasonable request.

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