Cardiovascular Diabetology

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Improving cardiovascular risk stratification: the role of abdominal obesity in predicting MACEs

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Abstract

Background Accurate cardiovascular risk (CVR) stratification remains challenging, particularly in identifying individuals with residual risk despite current screening tools. Abdominal obesity reflects visceral adipose tissue, which is metabolically active and strongly linked to pro-inflammatory and atherogenic states. This study aimed to evaluate the predictive utility of baseline cardiometabolic risk factors, with a particular focus on abdominal obesity as quantified by waist circumference (WC), alongside established 10-year CVR scores, for incident Major Adverse Cardiovascular Events (MACEs).

Methods We prospectively followed 736 outpatients (347 males, 389 females) from an Italian Internal Medicine Unit, initially free of MACEs. Baseline data included anthropometrics, biochemical markers, and calculated Framingham Risk Score (FRS) and SCORE2/SCORE2-OP. Abdominal obesity was defined according to the International Diabetes Federation criteria for Metabolic Syndrome (MetS) as a WC ≥ 94 cm in males and ≥ 80 cm in females. Incident MACEs were recorded during follow-up. Statistical analyses included t-tests, Chi-Square, ANOVA, and logistic regression.

Results Over a median follow-up of 84.9 months, 132 participants (17.9%) developed MACEs. Baseline abdominal obesity, present in 78.1% of the cohort, was significantly associated with incident MACEs (OR = 1.784, 95% CI = 1.04–3.118, $p = 0.038$), whereas BMI-defined obesity showed no such association ($p = 0.394$). Low HDL-cholesterol also emerged as a key predictor (OR = 1.672, 95% CI = 1.115–2.482, $p = 0.012$). In multivariate logistic regression, adjusted for age and other MetS components, abdominal obesity (OR = 2.2, 95% CI = 1.6–4.2, $p = 0.001$) and low HDL-c (OR = 1.9, 95% CI = 1.4–3.5, $p = 0.001$) remained robustly associated with MACEs. Notably, individuals within the SCORE2/SCORE2-OP 'Moderate-Risk' category, despite not being the highest risk overall, exhibited the highest baseline LDL-c levels and accounted for the largest proportion of MACEs (36.4%). Even among participants without baseline

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abdominal obesity, those who developed MACEs had significantly higher WC ($p < 0.0001$) and lower HDL-c ($p = 0.0078$) at baseline.

Conclusion Abdominal obesity and low HDL-c are potent, independent predictors of cardiovascular events, outperforming traditional markers like BMI. Together with the need of reaching LDL-c serum target levels, these biomarkers are crucial for unmasking the residual risk missed by current stratification models.

Introduction

The management of cardiovascular risk (CVR) represents one of the most complex challenges in contemporary clinical practice due to the multifactorial nature of its development [1], including the high prevalence of atherosclerosis [2–6], and the widespread adoption of unhealthy behaviours, such as smoking and Western dietary patterns [7, 8].

Despite significant pharmacological advancements to mitigate disease progression, the global burden of nearly 500 million affected patients and 18 million annual deaths [9–12] underscores the urgent need for a comprehensive strategy that prioritizes lifestyle modifications and the elimination of harmful habits [13–21]. Major clinical guidelines [22–25] consistently identify prevention as the cornerstone for reducing both atherosclerosis and its clinical consequences, including myocardial infarction (MI), stroke, transient ischemic attacks (TIA), heart failure (HF), and cardiac-related mortality. Accordingly, enhancing screening strategies to develop more accurate and widely deployable risk assessment tools, suitable even for non-clinical settings, is imperative for bolstering primary prevention on a broader scale.

Cardiovascular disease (CVD) mortality is predominantly attributed to atherosclerotic cardiovascular diseases (ASCVD), primarily ischemic heart disease (IHD)– accounting for approximately 49.2% of CVD deaths– and stroke.

Even though the past two decades have experienced a significant decline in CVD mortality, attributable to reductions in some risk factors along with improvements in acute treatment and secondary prevention, the rising prevalence of obesity and diabetes now threatens to reverse these gains. Metabolic Syndrome (MetS), a cluster of conditions including obesity, dyslipidaemia, impaired fasting glycemia, and arterial hypertension (AH), is a significant contributor, conferring a two-fold increased risk for cardiovascular events (CVE) [26]. Although declining smoking rates and widespread pharmacological treatment for AH and dyslipidaemia have had positive impacts, ASCVD, an inflammatory disease of medium and large arteries, remains the principal pathological substrate of IHD, ischemic stroke, and peripheral artery disease (PAD).

MetS and obesity are intrinsically linked to CVR through a complex interplay of molecular and systemic mechanisms [13]. Central to this nexus is visceral adiposity (VA), a metabolically active tissue that secretes a wide range of pro-inflammatory cytokines, adipokines, and reactive oxygen species, which collectively contribute to endothelial dysfunction (ED), oxidative stress, and a persistent state of low-grade systemic inflammation [27–29]. These processes are fundamental to the initiation and progression of atherosclerosis [30–32]. Nonetheless, the metabolic disturbances characteristic of MetS, notably insulin resistance, atherogenic dyslipidaemia (marked by elevated triglycerides, low High-Density Lipoprotein cholesterol, and often small, dense Low-Density Lipoprotein cholesterol particles), and elevated blood pressure (BP), further compromise vascular integrity and promote plaque instability [33, 34].

The pro-inflammatory environment generated by visceral adipose tissue (VAT) not only accelerates atherogenesis but also established a self-amplifying loop of vascular injury through immune activation, particularly via macrophage polarization. This inflammatory milieu promotes endothelial dysfunction and accelerates the development of unstable atheromatous plaques [29–31]. Beyond the pro-atherogenic effects of LDL-c, both the functional impairment and quantitative reduction of HDL-c, especially the pre-β HDL fraction, further exacerbate this process by compromising reverse cholesterol transport (RCT) [35–37]. Indeed, dysfunctional RCT has been independently associated with an increased risk of MACEs [38–40], proving that cholesterol efflux capacity is inversely associated with incident atherosclerotic CVD even in subjects that were free from cardiovascular disease at baseline [41, 42]. As ischemic damage evolves, microvascular dysfunction further compromises organ perfusion. For instance, in the kidney, altered perfusion disrupts the renin–angiotensin–aldosterone system (RAAS), worsening AH and proving the complex bidirectional relationship among ED, AH, and VAT [43].

In this study, we prospectively followed a subset of 736 subjects, free of major cardiovascular events at their initial evaluation, who participated in a follow-up assessment to identify incident MACEs. We aimed to determine if baseline cardiometabolic risk factors, with a particular emphasis on measures of abdominal obesity, alongside established 10-year CVR prediction scores– the Framingham Risk Score (FRS) and SCORE2/SCORE2-OP– could be associated with the development of these events, as well as their potential utility as predictive factors in clinical practice.

Material and methods

Study population

From May 2014 to April 2022, a total of 1,412 outpatients were evaluated for metabolic disorders in Internal Medicine Unit and their clinical, laboratory, and instrumental data were consecutively recorded in the electronic health register of Metabolic Diseases of the Department of Interdisciplinary Medicine, "Aldo Moro" University of Bari, Italy. Following their first evaluation, patients underwent routinary follow-ups, according to their clinical conditions and recommendations.

Exclusion criteria included previous MACEs diagnoses (i.e., stable or unstable angina, stroke, pulmonary embolism, acute coronary syndrome), history of cancer, chronic liver disease, and neurodegenerative disease.

Of the initial study population, 173 met the exclusion criteria for previous MACEs. A total of 40 subjects were further removed because of previous cancer diagnoses (i.e., colorectal cancer, liver cancer, stomach cancer). Additionally, a total of 83 subjects were removed from the final cohort because of alcohol-related chronic liver disease. Furthermore, 204 individuals were excluded due to incomplete data for key cardiometabolic features. Following a detailed data screening and outlier analysis, a total of 176 individuals were identified as significant outliers for their baseline values and were thus excluded from the follow-up cohort, reaching the total of 736 subjects enrolled in the present study (Supplementary Fig. 1).

In May 2024, patients were then re-evaluated by trained medical personnel, specifically investigating any MACEs that had occurred since their initial evaluation. All reported MACEs were further verified through hospital records.

The study protocol was approved by the Ethics Committee of the Azienda Ospedaliero-Universitaria Policlinico di Bari, (Bari, Italy), in accordance with the principles of the Declaration of Helsinki. Written informed consent for clinical data use was collected from all participants. Following the Ethics Committee guidelines, only subjects who were already 18 years old or older at first evaluation were included in the present study.

Clinical evaluation and anthropometric measurements

Anthropometric parameters including height, body weight and WC were obtained using standardized measurement procedures [44]. WC was measured at the midpoint between the lower ribs and the iliac crest. Values ≥ 94 cm in males and ≥ 80 cm in females were considered positive for MetS according to the 2006 International Diabetes Federation (IDF). Diagnosis of MetS was then formulated based on the simultaneous presence of positive WC alongside at least two of the following criteria: hypertriglyceridemia with Triglycerides (TGs) ≥ 150 mg/dL or under specific treatment, arterial hypertension with SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or under specific treatment, reduced HDL-c with HDL-c < 40 mg/dL in males and < 50 mg/dL in females or under specific treatment, FPG ≥ 100 or with a previously diagnosed T2D.

BP was determined after three consecutive evaluations, discarding the first one and calculating the average among the second and the third ones. Body Mass Index (BMI) was calculated as body weight (kg) divided by height squared (sqm); conditions of normal weight, overweight and obesity were identified according to BMI values of respectively 20.0–24.9, 25.0–29.9 and 30.0 kg/sqm.

Prediabetes (preDM), T2D and AH were diagnosed according to the criteria approved by the international community [45]. For preDM, the criteria were: fasting plasma glucose (FPG) ≥ 100 and ≤ 125 mg/dL and percentage of glycosylated haemoglobin (HbA1c) ≥ 5.7% and ≤ 6.4%. For T2D, the criteria were: HbA1c ≥ 6.5%, FPG ≥ 126 mg/dL and/or treatment for diabetes. AH was defined as systolic arterial blood pressure (SBP) ≥ 130 mmHg, diastolic arterial blood pressure (DBP) ≥ 85 mmHg and/or ongoing treatment with antihypertensive agents. Smoking was defined as the act of inhaling and exhaling the fumes of burning tobacco material, according to the most recent World Health Organization (WHO) definition [46]. SCORE2 (40–69 years old) [47]/SCORE2-OlderPersons (OP) (> 69 years old) [48] and 10-Years-FRS [49, 50] were obtained with the official online calculators respectively from the European Society of Cardiology (ESC) and the Framingham Heart Study (Supplementary Fig. 2).

Biochemical measurements

After overnight fasting, serum was collected for the measurement of standard biochemical markers of glucose and lipid metabolism, liver, renal, and thyroid function, as well as inflammation cards by standard biochemical methods.

Statistical analysis

Descriptive statistical analysis of study sample was performed, and their results were expressed as mean ± standard deviation (SD) and frequencies (%), depending on the nature of variables. Comparisons of socio-demographic and clinical parameters between two groups of interest were carried out with the t-test (for continuous variables) and the Pearson $\chi 2$ test (for categorical variables), after having verified their normal distribution. Comparisons between more than two groups were studied through one-way analysis of variance (ANOVA) followed by Bonferroni post-hoc test, where necessary. Contingency tables were used to visualize the association between categorical variables. ORs and 95% confidence intervals (CIs), according to the literature-based

Baptista-Pike method, were used to determine effect size. ORs adjusted for specific variables were calculated via Logistic Regression. ORs and CIs were graphically plotted in a blobbogram. The median time to MACEs development during the follow-up period was estimated using the Kaplan–Meier method.

p-values lower than 0.05 were considered significant. All the analyses were performed using NCSS 2020 Statistical Software, version 11.0.24 (NCSS, LLC Company) and GraphPad Prism, version 7.04 (GraphPad Software; San Diego, USA).

Results

Characterization of the study population

The final study cohort consisted of 736 participants (347 males and 389 females). We identified the baseline characteristics of these subjects, finding that 256 participants (34.8%) were smokers, 256 (34.8%) had T2D, and 363 (49.3%) were diagnosed with AH. Interestingly, 575 individuals (78.1%) exhibited an increased WC whereas, based on BMI, only 62.1% of the cohort could be classified as overweight or obese. Detailed baseline characteristics of the study population are presented in Table 1.

To further study patients' characteristics at baseline, we divided the overall study population in four subgroups, according to their CVR classes. Given the European composition of the study cohort, CVR stratification was performed using the SCORE2 and SCORE2-OP algorithms in 4 classes of risk. A total of 85 (11.5%) individuals were classified in the Low-Risk group, whereas 269 (36.5%) patients were categorized with Moderate-Risk, 196 (26.6%) with High-Risk and 186 (25.3%) with Very-High Risk (Supplementary Table 1).

Table 1 Characterization of the study population

Variable	n = 736 (347 M:389F)
Age (years; mean ± SD)	57.0 ± 14.3
MACEs during follow-up	132 (18.0%)
Smoke	256 (34.8%)
Type-2 Diabetes	256 (34.8%)
In Treatment for Diabetes	250 (34.0%)
Arterial Hypertension	363 (49.3%)
In Treatment for Hypertension	327 (44.4%)
Triglycerides positive criterion	159 (21.6%)
In Treatment for Hypertriglyceridemia	155 (21.1%)
HDL-cholesterol positive criterion	187 (25.4%)
In Treatment for Hypercholesterolemia	169 (23.0%)
Abdominal Obesity	575 (78.1%)
BMI ≥ 25 kg/sqm	457 (62.1%)
BMI 25– 29.9 kg/sqm	247 (33.6%)
BMI ≥ 30 kg/sqm	210 (28.5%)

Number, n; Male, M; Female, F; Standard Deviation, SD; Major adverse cardiovascular events, MACEs; High Density Lipoprotein-cholesterol, HDL-c; Body Mass Index, BMI; Waist circumference, WC; Metabolic Syndrome, MetS; glycosylated hemoglobin, HbA1c; Fasting Plasma Glucose, FPG; Arterial Hypertension, AH; Systolic Blood Pressure, SBP; Diastolic Blood Pressure, DBP; Triglycerides, TG

We then proceeded to study their cardiometabolic profile according to their CVR groups (Fig. 1). WC significantly increased along with the class of risk, ranging from 88.0 ± 12.9 in the Low-Risk group to 103.0 ± 12.3 in the Very High-Risk group, as shown in Fig. 1a (ANOVA $p < 0.001$). When considering the lipid profile, we first analysed parameters that are included in the SCORE2/SCORE2-OP algorithm. Total Cholesterol (TC) levels were significantly lower (ANOVA $p = 0.003$) in the Low-Risk group and in the Very High-Risk group (179.2 ± 34.7 and 176.4 ± 54.4, respectively), compared to the Moderate-Risk group and the High-Risk Group (190.0 ± 38.9 and 188.1 ± 36.5, respectively) as shown in Fig. 1b. Furthermore, HDL-c levels steadily decreased (ANOVA $p < 0.0001$) as the overall CVR increased (62.9 ± 13.9 in the Low-Risk group and 49.1 ± 13.8 in the Very-High Risk group, respectively), as shown in Fig. 1c. Nonetheless, when considering LDL-c, a parameter not included in the SCORE2/SCORE2-OP algorithms, we observed that individuals within the Moderate-Risk group presented the highest values (111.9 ± 35.5) compared to the other groups (ANOVA $p < 0.0001$), as showed in Fig. 1d.

At follow-up, 132 (17.9% of the overall cohort, 49.2% males) patients referred to have developed a MACE following their first evaluation, with a median time for CVE development of 84.9 months (Fig. 2).

When considering their respective classes of risk, a total of 9 patients (6.8% of the overall MACEs) were individuals within the Low-Risk group, 48 (36.4%) were within the Moderate-Risk group, 36 (27.3%) were previously classified in the High-Risk group and 39 (29.5%) were originally in the Very-High Risk group.

Cardiometabolic key factors for MACEs development

To further identify factors associated with MACEs development, we then divided our study cohort according to the presence of CVE and compared the two groups (Table 2). We observed that sex ($p = 0.631$), smoking habit ($p = 0.615$) or T2D diagnosis ($p = 0.920$) were not significantly altered between individuals who developed MACEs (EVENT group) and those who did not (NO EVENT group). Furthermore, we compared the clinical and biochemical biomarkers between the same groups, highlighting that individuals within the EVENT group were slightly older (59.6 ± 12.6 vs 56.4 ± 14.5, $p = 0.010$), compared to the NO EVENT group, and that no other factors were significantly changed between the two groups, except for AST levels (24.4 ± 11.3 vs 22.2 ± 7.6, $p = 0.037$). Interestingly, when comparing BMI levels, we observed that any potential classification using BMI was not altered between the two groups. Nonetheless, when considering the CVR predictors, only SCORE2/2OP

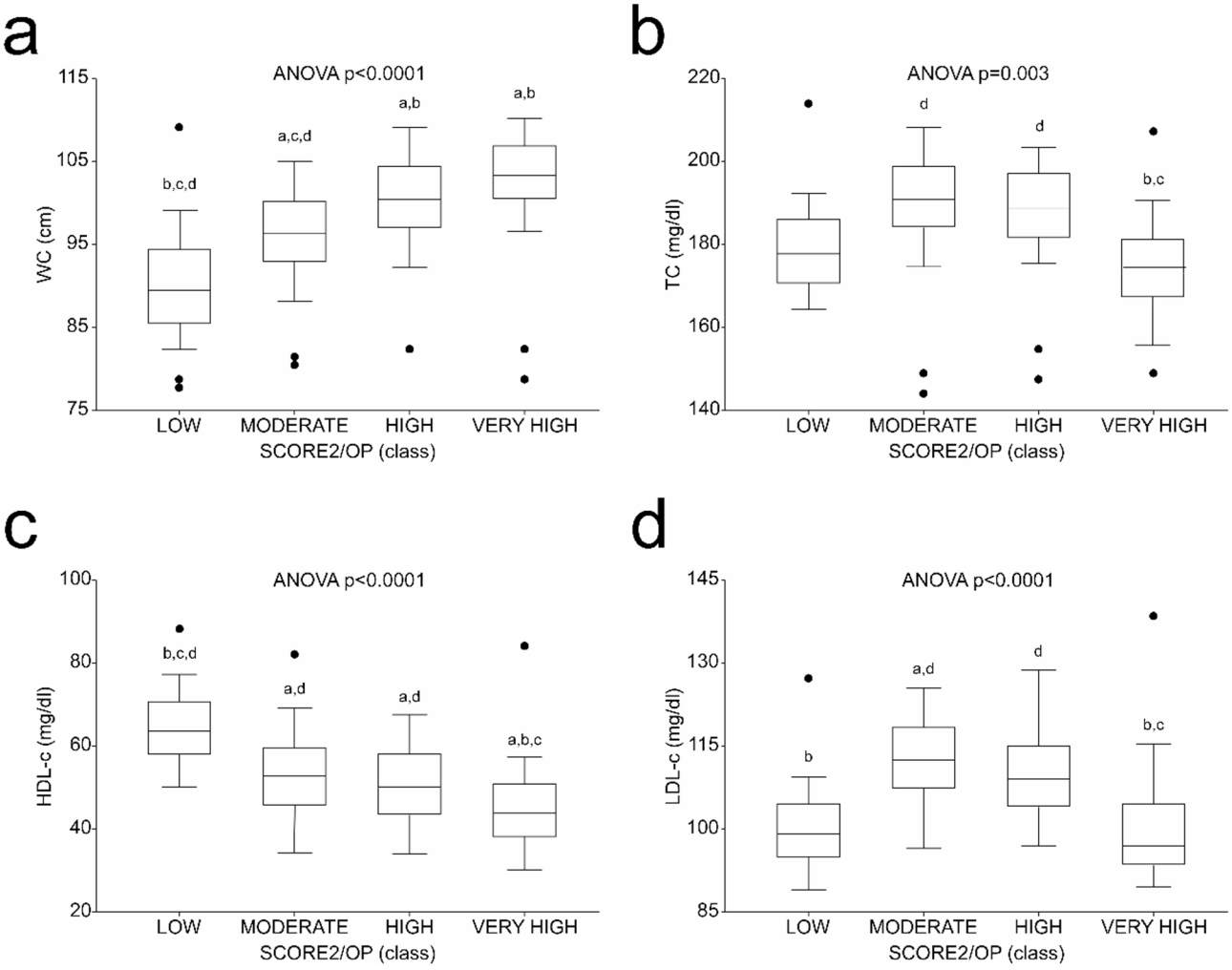

Fig. 1 Cardiometabolic biomarkers according to SCORE2/SCORE2-OP risk classes. Box plots show median (second quartile), first and third quartile. Tukey whiskers reach 1.5 times the interquartile distance or the highest or lowest point, whichever is shorter. Any data beyond the whiskers are shown as black dots. Comparisons were performed using ANOVA method. (*$p < 0.05$; ** $p < 0.01$). **a** Box plots of waist circumference according to SCORE2/SCORE2-OP risk classes; **b** Box plots of total cholesterol according to SCORE2/SCORE2-OP risk classes; **c** Box plots of HDL-c according to SCORE2/SCORE2-OP risk classes**d** Box plots of LDL-c according to SCORE2/SCORE2-OP risk classes. [a] indicates significance vs. Low-risk group; [b] indicates significance vs. Moderate-risk group; [c] indicates significance vs. High-risk group; [d] indicates significance vs. Very-high risk group. Abbreviations: Waist Circumference, WC; Total cholesterol, TC; High-density lipoprotein cholesterol, HDL-c; Low-density lipoprotein cholesterol, LDL-c

showed significance ($p = 0.037$), being higher in the EVENT group (11.4 ± 9.3) compared to the NO EVENT group (9.6 ± 8.1).

Abdominal obesity and HDL cholesterol define increased risk for MACEs regardless of age

Aiming to characterize the cardiometabolic risk profile for MACEs development, we then calculated the association between MACEs and single metabolic features of the MetS diagnosis (Fig. 3).

Compared to those in the NO EVENT group, individuals in the EVENT group with abdominal obesity exhibited a significantly higher risk for MACEs development (OR = 1.78, 95% CI = 1.04–3.12, $p = 0.038$). Furthermore, those with low HDL-c showed an increased risk for MACEs (OR = 1.67, 95% CI = 1.11–2.48, $p = 0.012$). Conversely, conditions like AH (OR = 1.39, 95% CI = 0.96–2.04, $p = 0.102$), impaired FPG (OR = 1.15, 95% CI = 0.79–1.66, $p = 0.482$) and hypertriglyceridemia (OR = 1.26, 95% CI = 0.81–1.93, $p = 0.3$), which were not linked with MACEs.

To strengthen our data, we performed a multivariate analysis for MACEs development in a two-step approach (Table 3). First, we considered all the MetS parameters plus obesity diagnosis according to BMI. We observed that abdominal obesity (OR = 1.9, 95% CI = 1.4–3.6, $p = 0.018$) and HDL-c (OR = 1.6, 95% CI = 1.3–3.4, $p = 0.019$) remained significant as in the previous analyses, while the other parameters were not significant (Table 3, Model 1). Subsequently, given the significant

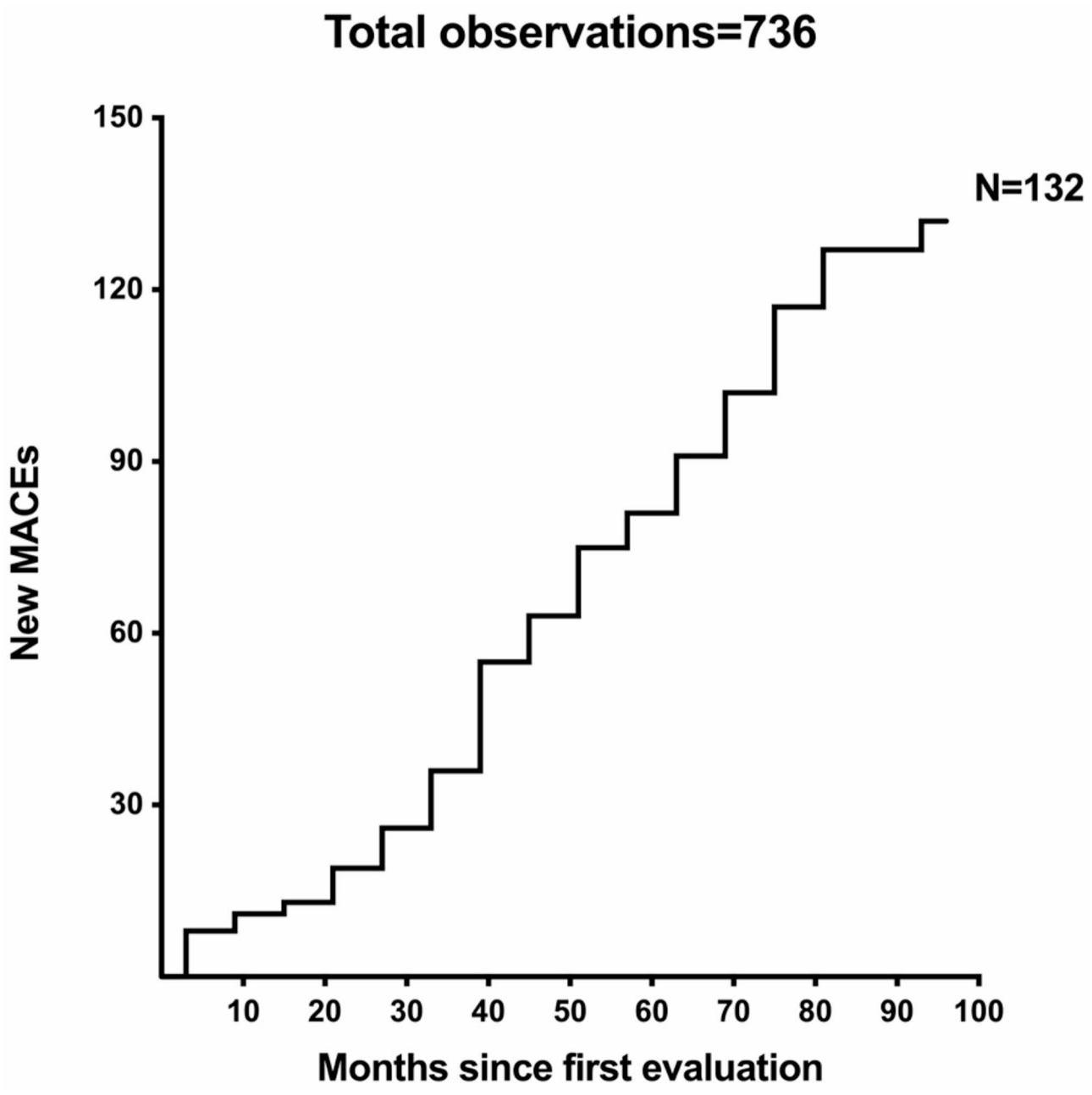

Fig. 2 MACEs distribution during follow-up time in our study cohort. The median time to MACEs development during the follow-up period, estimated using the Kaplan–Meier method, was 84.9 months.

difference in age between patients with and without CVEs, we refined the multivariate analysis further adjusting for age, finding that abdominal obesity (OR = 2.2, 95% CI = 1.6–4.2, $p = 0.001$) and HDL-c (OR = 1.9, 95% CI = 1.4–3.5, $p = 0.001$) remained significant. Nonetheless, hypertriglyceridemia was significant as well (OR = 1.6, 95% CI = 1.3–2.9, $p = 0.041$), conversely to the prior analysis (Table 3, Model 2).

To further explore risk factors independent of a pre-existing abdominal obesity diagnosis, we compared the cardiometabolic profiles of the 146 subjects (39.1% males) without abdominal obesity, stratified by MACE development. Notably, within this non-abdominally obese group, those who developed CVEs (n = 19) still had a significantly higher WC ($p < 0.0001$, Fig. 4a), and markedly lower HDL-c levels ($p = 0.0078$, Fig. 4c) than their counterparts. Differences in TC ($p = 0.0783$, Fig. 4b) and LDL-c ($p = 0.199$, Fig. 4d), though trending higher in the MACE group, were not statistically significant,

Table 2 Comparison of socio-anagraphic, clinical and biochemical variables between patients according to MACEs development during the follow-up period

	NO EVENT (n = 604; 282 M:322F)	EVENT (n = 132; 65 M:67F)	*p*-value
Socio-anagraphic assessment			
Age (years)	56.4 ± 14.5	59.6 ± 12.6	0.010*
Men	282 (46.7%)	65 (49.2%)	0.631
Females	322 (53.3%)	67 (50.8%)	
Smoke	207 (34.3%)	49 (37.1%)	0.615
Clinical assessment			
Waist Circumference (cm)	98.2 ± 14.9	99.5 ± 12.4	0.324
BMI (Kg/sqm)	27.2 ± 5.6	27.9 ± 5.6	0.240
BMI ≥ 25	368 (60.9%)	89 (67.4%)	0.195
BMI = 25– 29.9	200 (33.1%)	47 (35.6%)	0.295
BMI ≥ 30	168 (27.8%)	42 (31.8%)	0.394
Glucose (mg/dL)	101.8 ± 31.3	103.8 ± 28.7	0.514
HbA1c (mmol/mol)	41.2 ± 11.4	41.4 ± 12.1	0.836
Type-2 Diabetes	211 (34.9%)	45 (34.1%)	0.920
Total Cholesterol (mg/dL)	185.5 ± 42.3	181.4 ± 43.5	0.321
HDL (mg/dL)	55.2 ± 15.5	52.6 ± 16.5	0.090
LDL (mg/dL)	106.6 ± 33.9	104.4 ± 36.4	0.521
Triglycerides (mg/dL)	119.1 ± 67.3	132.7 ± 97.2	0.055
SBP (mmHg)	127.5 ± 16.9	130.5 ± 16.6	0.071
DBP (mmHg)	78.4 ± 10.8	79.2 ± 9.3	0.486
Heart Rate (bpm)	71.8 ± 10.6	72.0 ± 9.98	0.827
25-OH Vitamin D (ng/mL)	23.0 ± 11.4	22.8 ± 10.4	0.880
AST (U/L)	24.4 ± 11.3	22.2 ± 7.6	0.037*
ALT (U/L)	30.9 ± 16.1	30.2 ± 13.9	0.634
GGT (U/L)	35.0 ± 38.6	33.0 ± 28.1	0.576
ALP (U/L)	70.7 ± 22.3	71.4 ± 16.0	0.749
Framingham Score (%)	18.0 ± 17.4	21.1 ± 17.4	0.067
SCORE 2 / 2-OP (%)	9.6 ± 8.1	11.4 ± 9.3	0.037*

Data is presented as mean ± SD (Standard Deviation). Comparisons were performed by Student T- test for continuous variables. Comparisons between groups were performed according to Chi-Square Test. Statistical significance was assessed for *p*-values < 0.05. SCORE 2 was calculated for patients younger than 70 years; SCORE 2 OP was calculated for older subjects. Abbreviations: Major adverse cardiovascular events, MACEs; Male, M; Female, F; Body Mass Index, BMI; Glycosylated Hemoglobin, HbA1c; High-Density Lipoprotein, HDL; Low-Density Lipoprotein, LDL; Systolic Blood Pressure, SBP; Diastolic Blood Pressure, DBP; Aspartate Transferase, AST; Alanine Transferase, ALT; Gamma-Glutamyl Transpeptidase, GGT; Alkaline phosphatase, ALP. (*) $p < 0.05$

confirming the ability of WC and HDL cholesterol to define increased risk for MACE.

Discussion

Despite substantial advances in cardiovascular prevention, accurately identifying individuals at high risk for MACEs remains a pressing clinical challenge. Traditional risk stratification tools often fall short, particularly in patients without overt comorbidities, leading to underestimation of residual cardiovascular risk. This gap underscores the need for simple, reproducible, and clinically relevant predictors that can improve early identification and enable timely interventions. Against this backdrop, our study explored the prognostic utility of various metabolic and anthropometric markers in a real-world population without previous cardiovascular events, with the aim of uncovering which parameters could independently predict incident MACEs over a significant follow-up period.

A key finding of our perspective study is the clinical relevance and independent predictive power of abdominal adiposity, measured by WC. Notably, WC emerged as a superior predictor of MACEs compared to BMI, which failed to show a significant association in either unadjusted or adjusted models. This discrepancy underscores a well-established limitation of BMI: its inability to differentiate between fat compartments or adequately capture the profound metabolic risk conferred by abdominal fat. Conversely, WC provides a more accurate estimation of this metabolically active fat mass and its associated inflammatory and atherogenic burden [51–53]. Indeed, the dysfunctional adipose tissue characteristic of abdominal obesity is known to promote not only systemic metabolic disturbances but also to exacerbate arterial stiffness and adverse vascular remodelling, both pivotal contributors to the development and progression of hypertension and broader cardiovascular pathology. [28, 30–33, 54].

Crucially, the predictive value of WC for MACEs persisted after adjustment for key cardiometabolic confounders. Even when considering age, the association was not only preserved but strengthened, suggesting that the impact of VAT dysfunction extends beyond aging and other significant metabolic dysregulations. Notably, even among subjects classified as lean, higher WC levels were still observed in those who subsequently developed MACEs. This finding underscores the limitations of relying solely on current dichotomous WC cut-offs and highlights an urgent need for more personalized CVR screening strategies. Indeed, these results align with the evolving paradigm that characterizes abdominal obesity as a central contributor to vascular injury, operating both independently, and synergistically, with traditional risk factors, and should be considered as a parameter for modern risk scoring systems, which traditionally do not consider it but instead opt just for recommendations [29, 55–57].

In parallel, low HDL-c levels emerged as another robust and independent predictor of MACEs in our cohort. Like WC, in both adjustment for cardiometabolic factors and age, reduced HDL-c was significantly associated with cardiovascular events. This consistent predictive capacity across diverse models strengthens the hypothesis that HDL-c as well exerts multifaceted atheroprotective effects– including anti-inflammatory, antioxidative, anti-apoptotic, and endothelial-stabilizing properties– that operate independently of a patient's age, glycaemic status, or hemodynamic burden, and extend far beyond its

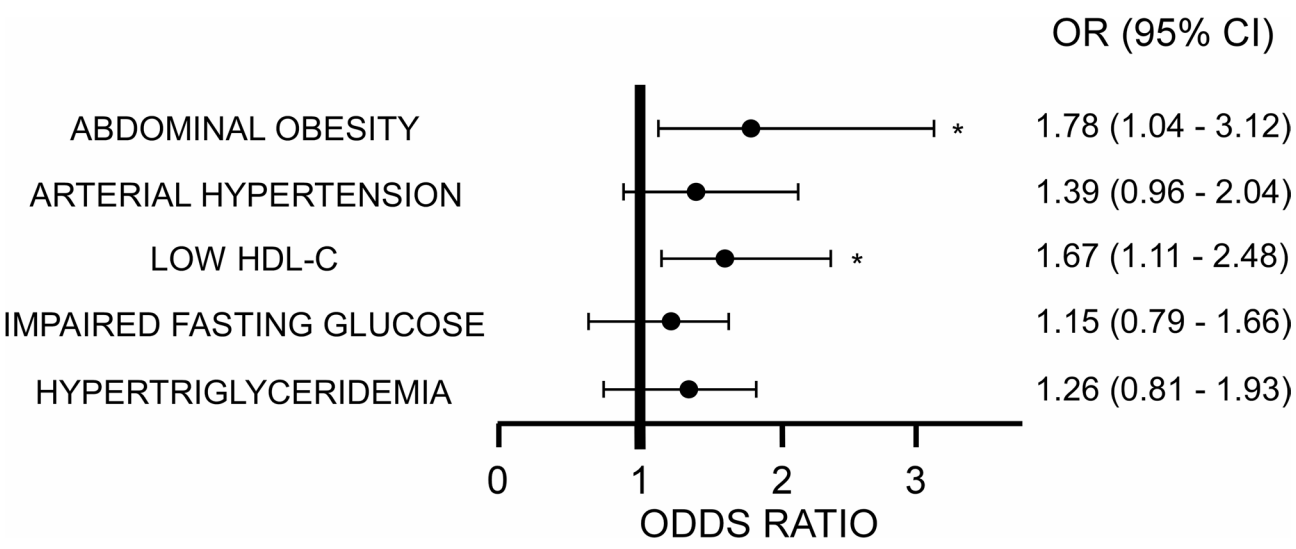

Fig. 3 Association of CVE and cardiometabolic conditions. Odds Ratios for patients with specific cardiometabolic risk factors are represented. Contingency tables, OR value and 95% C.I. are reported. Fisher's Exact test was calculated and $p < 0.05$ was considered significant. Abbreviations: Odds Ratio, OR; Confidence Interval, CI; High Density Lipoprotein-cholesterol, HDL-c; Body Mass Index, BMI

Table 3 Multivariate analyses for major cardiometabolic markers and MACEs development

	Model 1			Model 2		
Variable	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Abdominal Obesity	1.9	1.4–3.6	0.018*	2.2	1.6–4.2	0.001**
Arterial Hypertension	1.5	0.9–2.5	0.067	1.4	0.9–2.5	0.066
Low HDL-c	1.6	1.3–3.4	0.019*	1.9	1.4–3.5	0.001**
Impaired FPG	1.1	0.6–1.7	0.511	1.0	0.4–1.4	0.691
Hypertriglyceridemia	1.1	0.8–1.5	0.589	1.6	1.3–2.9	0.041*
BMI ≥ 30 kg/Sqm	1.2	0.5–1.9	0.358	1.5	0.8–2.4	0.068

Major adverse cardiovascular events, MACEs; Body Mass Index, BMI; Glycosylated Hemoglobin, HbA1c; High-Density Lipoprotein, HDL; Low-Density Lipoprotein, LDL; Systolic Blood Pressure, SBP; Diastolic Blood Pressure, DBP; Aspartate Transferase, AST; Alanine Transferase, ALT; Gamma-Glutamyl Transpeptidase, GGT; Alkaline phosphatase, ALP. (*) $p < 0.05$; (**) $p < 0.01$

classical role in RCT [58, 59]. The sustained predictive value of HDL-c underscores its utility as a crucial marker of residual risk, particularly valuable for identifying individuals, even non-obese ones or those without overt comorbidities, who might otherwise evade detection by conventional risk scoring systems [60, 61].

Interestingly, our analysis of SCORE2-defined risk categories revealed a non-linear distribution of LDL-c and event incidence. Paradoxically, patients classified within the Moderate-Risk category displayed significantly higher LDL-c levels compared to those in the Low, High, and Very High-Risk groups and were, indeed, the first subgroup of patients in our cohort to exhibit WC levels above the threshold for MetS. Crucially, it was this Moderate-Risk subgroup who experienced the highest number of cardiovascular events during follow-up. This counterintuitive pattern challenges the assumption that event incidence always scales linearly with globally calculated risk and suggests a potential underestimation of LDL-driven risk within intermediate risk categories by composite scores, proving once again the significance of WC as a standalone risk factor. A plausible interpretation is that markedly elevated LDL-c may exert a particularly pivotal and aggressive role in the earlier pathophysiological phases of atherogenesis, perhaps before the accumulation of multiple other comorbidities that would eventually elevate global risk scores to *high* or *very high* [62, 63]. These findings raise important questions about the sufficiency of composite scoring systems to fully capture the impact of strongly influential single-parameter vulnerabilities.

Limitations of the study must be addressed as well. First, as with all observational studies, the associations found between WC/HDL-c and MACEs do not definitively prove causation. Despite adjustments for confounders, residual confounding can never be entirely excluded. Nonetheless, the single-centre nature and patient population (European) may limit the generalizability of the findings to other populations (e.g., different ethnicities, primary care settings, or general populations without pre-existing metabolic evaluations). Finally, at the recruitment time, no direct estimation of visceral fat

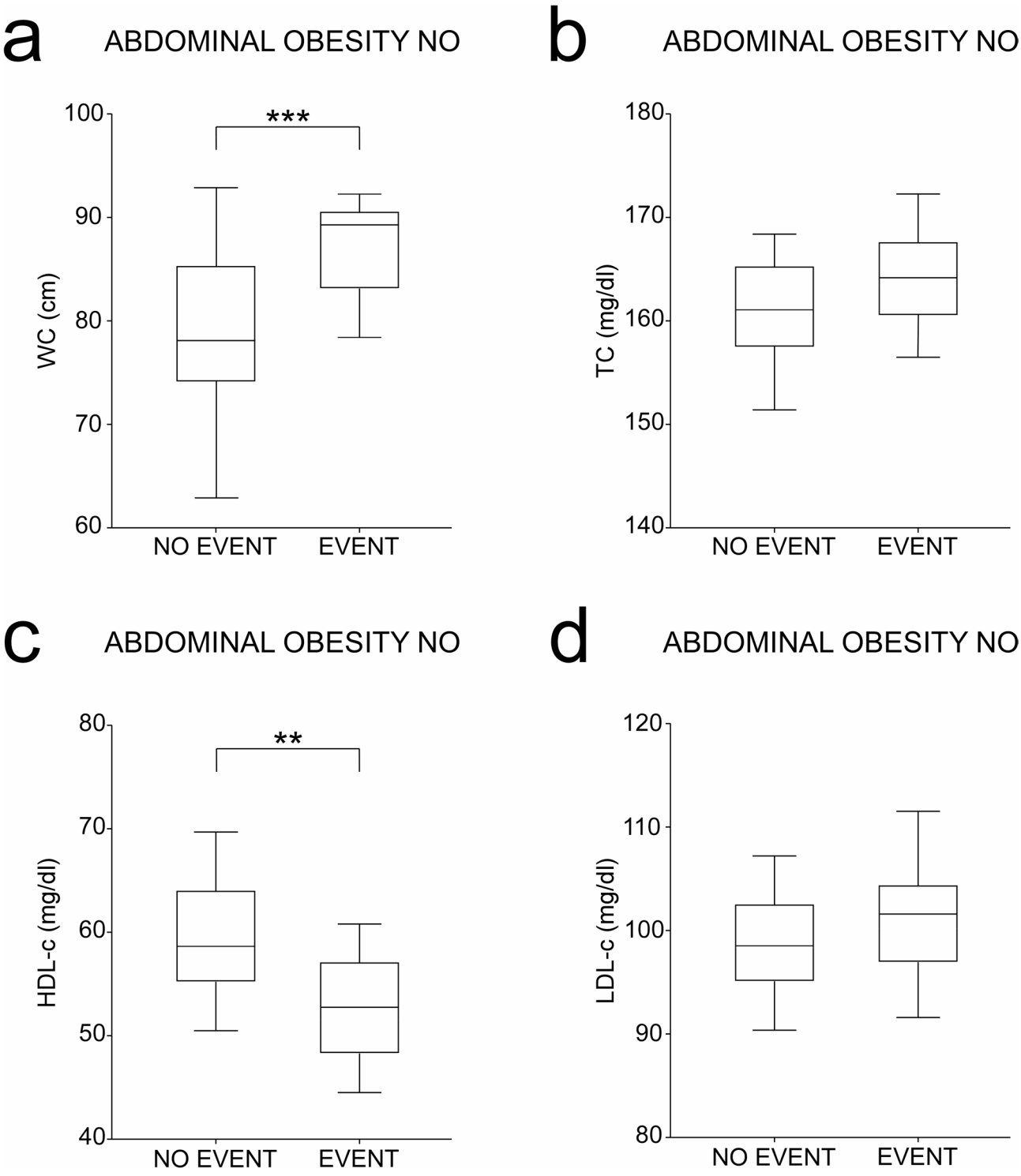

Fig. 4 Comparison of waist circumference and lipid profile in individuals without abdominal obesity, based on CVE development. Box plots show median (second quartile), first and third quartile. Tukey whiskers reach 1.5 times the interquartile distance or the highest or lowest point, whichever is shorter. Any data beyond the whiskers are shown as black dots. Comparisons were performed using Students' t-test. (** $p < 0.01$, *** $p < 0.001$). **a** Box plots of waist circumference according to MACE development; **b** Box plots of total cholesterol according to MACE development; **c** Box plots of HDL-c according to MACE development; **d** Box plots of LDL-c according to MACE development. Abbreviations: Major adverse cardiovascular events, MACE; Waist circumference, WC; Total cholesterol, TC; High-density lipoprotein cholesterol, HDL-c; Low-density lipoprotein cholesterol, LDL-c

was performed since Magnetic Resonance Imaging (MRI) scan was not included in the approved protocol.

Taken together, our findings underscore the pivotal role of WC as an accurate anthropometric marker of CVR. Its independent predictive capacity, demonstrated across adjusted models and even in lean subjects, confirms that abdominal obesity contributes to cardiovascular risk through multifaceted mechanisms that extend beyond traditional metabolic disturbances. Likewise, reduced HDL-c levels consistently maintained statistical significance as an independent predictor of MACEs, highlighting their critical role not only as a mere biomarker but also as a potential indicator of underlying vascular health and protective mechanisms.

These observations suggest a compelling need for a reappraisal of current CVR stratification paradigms in primary prevention. Future mechanistic studies exploring the nuances of HDL-c particle functionality (beyond mere concentration) and the specific VAT-derived cytokine and adipokine profiles most linked to MACEs are warranted. Abdominal obesity and low HDL-c are potent, independent predictors of cardiovascular events, outperforming traditional markers like BMI. Together with the need of reaching LDL-c serum target levels, these biomarkers are crucial for unmasking the residual risk missed by current stratification models. Their systematic integration into routine clinical assessment, together with therapeutic strategies aimed at reducing abdominal adiposity, could significantly improve the identification of individuals at higher risk, particularly those with subclinical atherogenic dysfunction or those whose risk might be underestimated by existing composite scores alone.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

Conceptualization, Lucilla Crudele and Antonio Moschetta; Methodology-visualization, Carlo De Matteis and Stefano Petruzzelli; Software-formal analysis, Carlo De Matteis, Stefano Petruzzelli, Giusi Graziano, Ersilia Di Buduo, Fabio Novielli and Salvatore Cantatore; Investigation, Carlo De Matteis, Stefano Petruzzelli, Lucilla Crudele and Antonio Moschetta; Data curation, Carlo De Matteis, Stefano Petruzzelli and Giusi Graziano; Writing—original draft preparation, Carlo De Matteis and Stefano Petruzzelli; Writing—review and editing, Maria Arconzo, Marica Cariello, Elsa Berardi, Marilina Florio and Gianfranco Antonica; Supervision, Lucilla Crudele and Antonio Moschetta; Project administration, Lucilla Crudele and Antonio Moschetta; Funding acquisition, Lucilla Crudele and Antonio Moschetta. All authors have read and agreed to submit the current version of the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee (Interdisciplinary Department of Medicine; n. 311, MSC/PBMC/2015, approved on 12 January 2015) of the Azienda Ospedaliero-Universitaria Policlinico di Bari (Bari, Italy) in accordance with the requirements of the Declaration of Helsinki. In accordance with the approved Ethics Committee, only patients who were already 18 years old or older were included. Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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