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Kardiometabolinė rizika: uždegimo, metabolinio sindromo ir ankstyvų širdies struktūrinių pokyčių sąsajos

Cardiometabolic Risk: Associations Between Inflammation, Metabolic Syndrome, and Early Cardiac Structural Remodelling

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ABSTRACT

Background and Aims: Body mass index (BMI) is widely used to assess cardiometabolic risk, however, it does not fully capture its heterogeneity. This study aims to examine cardiometabolic risk across obese and non-obese individuals, focusing on how anthropometric measures, metabolic markers, and systemic inflammation interact to influence cardiometabolic risk.

Methods: This cross-sectional analysis included 9,891 adults from the Lithuanian High Cardiovascular Risk Program (mean age 53.5 ± 6.5 years). Participants underwent standardized anthropometric, biochemical, and echocardiographic assessments. Multivariable regression models examined predictors of cardiometabolic outcomes. Unsupervised k-means clustering identified cardiometabolic phenotypes based on adiposity, metabolic, and inflammatory parameters.

Results: Of participants, 61.5% were obese. Compared with non-obese individuals, obese participants had higher waist circumference, systolic blood pressure, fasting glucose, triglycerides, and high-sensitivity C-reactive protein (hsCRP), and lower high-density lipoprotein cholesterol (all $p<0.001$). Log-transformed hsCRP independently predicted fasting glucose among obese individuals ($\beta=0.105$, $p<0.001$) but not in non-obese participants, with significant interaction ($\beta=0.126$, $p<0.001$). Metabolic syndrome was prevalent in both obese (89.7%) and non-obese (76.2%) groups. LVH was present in 45.1% overall and 38.5% of non-obese individuals. Waist circumference (OR 1.01 per cm, 95% CI 1.01–1.02) and systolic blood pressure (OR 1.01 per mmHg, 95% CI 1.01–1.02) were the strongest independent predictors of left ventricular hypertrophy (LVH). Clustering identified four phenotypes, including an inflamed high-triglyceride group characterized by moderate BMI with elevated triglycerides and hsCRP.

Conclusions: Cardiometabolic risk extends beyond BMI-defined obesity. Inflammation was more strongly associated with metabolic dysfunction in obese individuals, while central adiposity and blood pressure independently predicted LVH irrespective of BMI. These findings suggest that routine incorporation of waist circumference and inflammatory profiling into cardiometabolic risk assessment may identify high-risk individuals overlooked by BMI-based classification.

Keywords: Body mass index; metabolic syndrome; C-reactive protein; left ventricular hypertrophy; phenotypes; central obesity.

SANTRAUKA

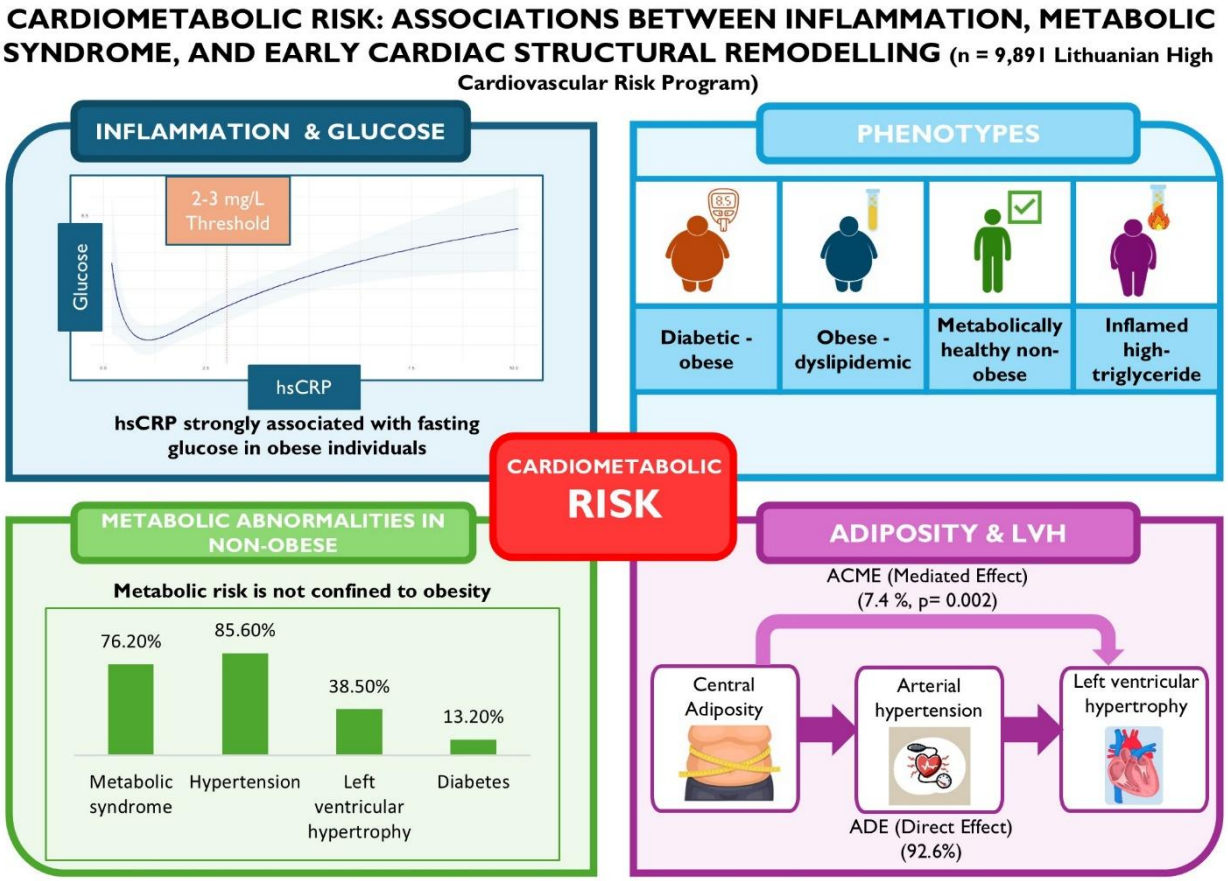
Įvadas ir tikslai: Kūno masės indeksas (KMI) plačiai naudojamas vertinant kardiometabolinę riziką, tačiau jis nevisiškai atspindi jos heterogeniškumą. Šio tyrimo tikslas – įvertinti kardiometabolinę riziką nutukusių ir nenutukusių asmenų grupėse, atkreipiant dėmesį į antropometrinių rodiklių, metabolinių žymenų ir sisteminio uždegimo tarpusavio sąveiką bei jų įtaką tiriamųjų kardiometabolinei rizikai.

Metodai: Į šį vienmomentinį skerspjūvio tyrimą buvo įtraukti 9891 tiriamieji iš Lietuvos didelės širdies ir kraujagyslių ligų rizikos programos (vidutinis tiriamųjų amžius 53,5 ± 6,5 metų). Visiems tiriamiesiems buvo atliktas standartizuotas antropometrinis, biocheminis ir echokardiografinis ištyrimas. Kardiometabolinių baigčių prognozavimui taikyti daugialypės regresijos modeliai. Kardiometaboliniai fenotipai identifikuoti, atsižvelgiant į tiriamųjų antropometrinius, metabolinius ir uždegiminius rodiklius, naudojant neprižiūrimą k-vidurkių klasterinę analizę.

Rezultatai: Iš visų dalyvių 61,5 % buvo nutukę. Lyginant su nenutukusiais asmenimis, nutukusiems nustatytos didesnės liemens apimties, sistolinis kraujospūdis, gliukozės koncentracijos nevalgius, trigliceridų koncentracijos ir didelio jautrumo C reaktyvaus baltymo (dj-CRB) vertės, bei mažesnė didelio tankio lipoproteinų cholesterolio (DTL-C) koncentracija ($p < 0,001$). Logaritmiškai transformuotas dj-CRB buvo nepriklausomas gliukozės koncentracijos nevalgius prognostinis veiksnys nutukusiųjų grupėje ($\beta = 0,105$; $p < 0,001$), tačiau nenutukusiųjų grupėje ši sąsaja nebuvo statistiškai reikšminga. Nustatyta reikšminga dj-CRB ir nutukimo sąveika ($\beta = 0,126$; $p < 0,001$). Metabolinis sindromas buvo dažnas tiek nutukusių (89,7 %), tiek nenutukusių pacientų (76,2 %) grupėse. Kairiojo skilvelio hipertrofija (KSH) nustatyta 45,1 % visų tiriamųjų ir 38,5 % nenutukusių asmenų. Liemens apimtis (ŠS 1,01; 95 % PI 1,01–1,02) ir sistolinis kraujospūdis (ŠS 1,01; 95 % PI 1,01–1,02) buvo stipriausi nepriklausomi KSH prognostiniai veiksniai. Klasterinė analizė identifikavo keturis kardiometabolinius fenotipus, tarp jų – uždegiminį aukštos trigliceridų koncentracijos fenotipą, kuriam būdingas vidutinis KMI, tačiau reikšmingai padidėjusi trigliceridų ir dj-CRB koncentracija.

Išvados: Kardiometabolinė rizika nepakankamai apibrėžiama KMI apibūdinamo nutukimo. Sisteminis uždegimas yra stipriau susijęs su metaboliniais sutrikimais nutukusių asmenų grupėje, o centrinis (pilvinis) nutukimas bei arterinis kraujospūdis nepriklausomai prognozuoja kairiojo skilvelio hipertrofiją nepaisant KMI verčių. Šie rezultatai rodo, kad įtraukus liemens apimties matavimą ir sisteminio uždegimo biožymenų vertinimą į rutininį kardiometabolinės rizikos ištyrimą, galima identifikuoti didelės rizikos asmenis, kurie lieka neatpažinti remiantis vien KMI pagrįsta rizikos klasifikacija.

Raktažodžiai: kūno masės indeksas; metabolinis sindromas; C reaktyvusis baltymas; kairiojo skilvelio hipertrofija; fenotipai; centrinis (pilvinis) nutukimas.



GRAPHICAL ABSTRACT

In a large cohort from the Lithuanian High Cardiovascular Risk Prevention Programme (n = 9,891), central adiposity, dyslipidaemia, hyperglycaemia, and systemic inflammation emerged as interrelated determinants of cardiometabolic risk that are not fully captured by BMI alone. hsCRP independently predicted fasting glucose, with a significantly stronger association among obese individuals, indicating that adiposity modifies the metabolic impact of systemic inflammation. Notably, cardiometabolic abnormalities and metabolic syndrome were highly prevalent even among non-obese participants, supporting the existence of metabolically high-risk phenotypes beyond BMI-defined obesity. Finally, central adiposity and systolic blood pressure were the strongest independent predictors of left ventricular hypertrophy, highlighting the central role of visceral adiposity and hemodynamic load in early cardiac remodeling. These findings support the incorporation of waist circumference and metabolic – inflammatory profiling into routine cardiometabolic risk assessment to improve identification of high-risk individuals who may be overlooked by BMI-based classification alone.

Abbreviations: hsCRP, high-sensitivity C-reactive protein; LVH, left ventricular hypertrophy; ACME, average causal mediation effect; ADE, average direct effect.

ABBREVIATIONS

AHA – American Heart Association

AIC – Akaike Information Criterion

ASCVD – Atherosclerotic Cardiovascular Disease

BMI – Body Mass Index

BP – Blood Pressure

BSA – Body Surface Area

CI – Confidence Interval

CRP – C-reactive Protein

CVD – Cardiovascular Disease

ESC – European Society of Cardiology

HDL-C – High-Density Lipoprotein Cholesterol

hsCRP – High-Sensitivity C-reactive Protein

IL-1 – Interleukin-1

IL-6 – Interleukin-6

IQR – Interquartile Range

LDL-C – Low-Density Lipoprotein Cholesterol

LitHiR – Lithuanian High Cardiovascular Risk Prevention Programme

LVH – Left Ventricular Hypertrophy

LVMI – Left Ventricular Mass Index

MACE – Major Adverse Cardiovascular Events

MetS – Metabolic Syndrome

MHO – Metabolically Healthy Obesity

MUNW – Metabolically Unhealthy Normal Weight

NCEP ATP III – National Cholesterol Education Program Adult Treatment Panel III

NHANES – National Health and Nutrition Examination Survey

OR – Odds Ratio

ROC – Receiver Operating Characteristic

SD – Standard Deviation

SCORE2 – Systematic Coronary Risk Evaluation 2

TG – Triglycerides

TNF-α – Tumor Necrosis Factor Alpha

VIF – Variance Inflation Factor

VLDL – Very Low-Density Lipoprotein

WC – Waist Circumference

WHO – World Health Organization

WHR – Waist-to-Hip Ratio

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1. INTRODUCTION

Body mass index (BMI), although widely used to define obesity and stratify cardiometabolic risk, fails to fully capture the heterogeneity of metabolic and cardiovascular risk profiles across individuals [1]. It does not distinguish between fat mass and lean mass, nor does it account for fat distribution, particularly visceral adiposity, which plays a central role in metabolic dysfunction and cardiovascular remodeling**.** As a result, BMI alone may misclassify individuals' cardiometabolic risk.

Adult obesity has more than doubled since 1990 and is now firmly established as a major risk factor for arterial hypertension, dyslipidaemia, type 2 diabetes mellitus (T2DM), adverse cardiovascular outcomes and premature mortality [1,2]. While many individuals with obesity have the expected dysregulated biochemical profiles – not all do. A subgroup of obese individuals that maintain a relatively favourable metabolic profile is often referred to as "metabolically healthy obesity" (MHO) [3], although recent analysis demonstrated that no obesity phenotype can be considered metabolically benign, as even individuals with MHO demonstrate a substantially increased risk of cardiometabolic multimorbidity compared with normal-weight counterparts [4].

However, individuals with non-obese BMI may nonetheless exhibit significant metabolic abnormalities [5]. A large systematic review including over 400,000 people with normal BMI found that 26.78% of them exhibited one or more metabolic abnormalities consistent with metabolic syndrome criteria or related definitions [5]. These findings underscore that normal BMI does not necessarily indicate metabolic health and highlight the limitations of BMI-based risk stratification.

Central adiposity, often measured by waist circumference (WC), waist-to-hip ratio, or waist-to-height ratio, has emerged as a stronger predictor of cardiometabolic risk than BMI alone. Visceral adipose tissue differs from subcutaneous fat in its metabolic and endocrine activity, exhibiting increased lipolytic activity and secreting pro-inflammatory cytokines and adipokines that promote insulin resistance, dyslipidaemia, endothelial dysfunction, and atherosclerosis [1, 2]. According to the 2021 American Heart Association Scientific Statement, larger waist circumference is independently associated with cardiometabolic disease and mortality, regardless of a person's BMI [1]. A recent cross-sectional study demonstrated that both BMI and waist circumference serve as independent predictors of above-average cardiovascular risk as assessed by the SCORE2 and SCORE2-OP calculators, with waist circumference providing additional predictive value beyond BMI [6]. Consequently, WC helps more accurately identify high-risk individuals in whom BMI might underestimate cardiometabolic risk.

A key mechanistic pathway linking adiposity – particularly visceral adiposity – to metabolic dysfunction and cardiovascular disease is chronic low-grade systemic inflammation. Several recent observational studies have established that elevated high-sensitivity C-reactive protein (hsCRP)

levels are independently associated with increased risk of major adverse cardiovascular events (MACE), cardiovascular mortality, and all-cause mortality, even after adjustment for traditional risk factors including BMI [7]. These findings support hsCRP as a marker of cardiometabolic risk, although these associations appear to differ across adiposity phenotypes [7,8].

In addition to metabolic disturbances, excess adiposity and hypertension contribute to early structural cardiac remodeling, most notably left ventricular hypertrophy (LVH), that may develop long before overt clinical disease becomes apparent [9, 10]. A 2024 population-based cardiac imaging study demonstrated that central obesity is linked to increased left ventricular wall thickness even among non-obese adults, putting an emphasis on fat distribution rather than overall body weight as a key factor of early myocardial remodeling [11]. Finally, while hypertension remains the main determinant of LVH, abdominal adiposity provides additional predictive value beyond BMI alone, suggesting that reliance on BMI alone may fail to identify individuals with early subclinical cardiac damage.

Taken together, these observations indicate that cardiometabolic risk is determined by complex interactions among adiposity distribution, metabolic abnormalities, inflammatory processes, and cardiovascular remodeling, which are not fully captured by BMI-based classification. In particular, it is unclear whether systemic inflammation differentially associates with metabolic disturbances according to adiposity status and to what extent central adiposity contributes to LVH independently of BMI-defined obesity.

2. KNOWLEDGE GAPS AND STUDY RATIONALE

Body mass index (BMI) remains the primary clinical tool for obesity assessment but fails to capture substantial heterogeneity in cardiometabolic risk. Central adiposity and systemic inflammation are increasingly recognized as important determinants of metabolic dysfunction and cardiovascular risk, yet their integrated effects – and particularly whether adiposity modifies the metabolic impact of inflammation – remain insufficiently characterized in preventive cardiology populations. Moreover, while left ventricular hypertrophy represents a key marker of subclinical cardiovascular damage, the relative contributions of central adiposity, inflammatory activity, and metabolic abnormalities to cardiac remodeling beyond BMI are yet to be fully defined.

Data-driven approaches integrating anthropometric, metabolic, inflammatory, and cardiac structural parameters may provide improved risk characterization, but remain underexplored in large preventive cohorts. Addressing these gaps may enable more precise and accurate identification of high-risk individuals beyond BMI-based classification.

Therefore, this study aimed to examine cardiometabolic risk across obese and non-obese individuals, with a focus on how anthropometric measures, metabolic markers, and systemic inflammation interact to influence cardiometabolic risk. The study's objectives were:

1. To compare metabolic and inflammatory markers between obese and non-obese individuals.
2. To evaluate the association between systemic inflammation (hsCRP) and metabolic abnormalities across different adiposity categories.
3. To determine whether central adiposity and blood pressure are associated with left ventricular hypertrophy independently of BMI.
4. To identify cardiometabolic phenotypes within BMI categories based on anthropometric, metabolic, and inflammatory characteristics.

We hypothesized that (1) systemic inflammation would be more strongly associated with metabolic disturbances in obese than in non-obese individuals; (2) central adiposity and blood pressure would independently predict left ventricular hypertrophy beyond BMI; and (3) distinct cardiometabolic phenotypes could be identified within BMI categories, reflecting metabolic heterogeneity that is not captured by BMI alone.

3. LITERATURE OVERVIEW

3.1. Metabolic Syndrome

Metabolic syndrome, which is characterized by a constellation of metabolic abnormalities, including central obesity, insulin resistance, arterial hypertension, and dyslipidaemia, poses a significant risk for the development of atherosclerotic cardiovascular diseases, adverse cardiovascular outcomes and premature mortality [12]. Although several definitions of metabolic syndrome are used in research, a recent comparison suggested that the NCEP ATP III criteria may perform better than the IDF criteria when identifying individuals at higher atherosclerotic cardiovascular risk, especially in overall higher-risk populations – patients with MetS consistent with NCEP ATP III had higher ASCVD risk scores than those with IDF (10.63 ± 10.989 vs. 9.50 ± 9.357) and NCEP ATP III was recognized to have better overall performance in terms of specificity, accuracy, sensitivity and positive and negative predictive values in higher ASCVD risk score categories [13].

The clinical importance of MetS lies in the fact that these defining metabolic abnormalities do not simply add up; rather, together they create a pro-atherogenic, pro-inflammatory, and pro-thrombotic internal environment that accelerates vascular ageing and promotes cardiovascular disease [14]. More recent cohort studies have further defined these associations, showing that metabolic syndrome is linked to approximately a twofold increase in myocardial infarction risk: a Swedish cohort and meta-analysis study, found that normal-weight individuals with MetS had higher risk of myocardial infarction (HR 2.0, 95% CI 1.51–2.64) and stroke (HR 1.63, 95% CI 1.17–2.28). Importantly, the risk increased progressively with the accumulation of metabolic syndrome components, which supports the concept of a cumulative cardiometabolic burden [15].

MetS is now a major global public health issue. An up-to-date global analysis, published in *Nature*

Communications in 2025, estimated that in 2023 approximately 1.54 billion adults worldwide were living with metabolic syndrome [16]. In the analysis, between 2000 and 2023 prevalence rose in both sexes and across nearly all countries, reaching 31.0% in women and 25.7% in men globally in 2023 [16]. The burden increased with age, urbanization, and national income level, which is consistent with the broader shift toward sedentary lifestyles, calorie-denser diets, and increasing adiposity worldwide [16,17]. These data support the idea that MetS is no longer a condition seen only in selected high-risk groups, but rather a widespread and growing manifestation of modern cardiometabolic disease.

Lithuanian data are consistent with this global picture. Earlier population-based data from Kaunas reported that using the World Health Organization definition of metabolic syndrome, it was identified in 11.3% of men and for 9.4% of women, for 19.4% of men and for 26.3% of women using the Adult Treatment Panel III definition, and for 30.0% of men and for 37.7% of women using the International Diabetes Federation definition [18]. More recent Lithuanian reports from middle-aged prevention cohorts continue to show a high burden of metabolic and cardiovascular risk factors [19], while nationwide 2025 data on cardiovascular–kidney–metabolic syndrome suggest that a substantial proportion of adults aged 40 years and older already have advanced metabolic-cardiovascular disease [20]. Taken together, these findings suggest that MetS remains highly relevant in Lithuania, both as a marker of current vascular health and risk, and as an indicator of future diabetes and cardiovascular disease. For this reason, understanding MetS as a heterogeneous syndrome with different phenotypic expressions is important in both research and clinical practice.

3.2. Dyslipidaemia

Dyslipidaemia, particularly elevated triglycerides and reduced high-density lipoprotein cholesterol (HDL-C), play a central role in the development and progression of atherosclerotic cardiovascular disease, reflecting an underlying state of metabolic and vascular dysfunction [14]. In addition to traditional lipid abnormalities such as elevated low-density lipoprotein cholesterol (LDL-C), atherogenic dyslipidaemia – characterized by increased triglycerides, low HDL-C, and a predominance of small dense LDL particles – is strongly associated with insulin resistance and metabolic syndrome [21].

Triglyceride-rich lipoproteins (TRLs), including very low-density lipoproteins (VLDL) and their remnants, have been increasingly recognized as directly atherogenic. These particles can penetrate the arterial wall, become retained within the intima, and contribute to foam cell formation and plaque development, independent of LDL-C levels [21]. Elevated triglycerides are also associated with increased production of remnant cholesterol, which has been shown to be causally linked to ischemic heart disease in genetic studies [22].

Low HDL-C further contributes to atherogenesis through impaired reverse cholesterol transport and loss of anti-inflammatory, antioxidant, and endothelial-protective effects. Beyond its role in lipid transport, HDL exerts multiple vascular protective functions, which include inhibition of LDL oxidation, reduction of endothelial adhesion molecule expression, and promotion of nitric oxide production [23]. Reduced HDL-C levels are therefore associated not only with lipid imbalance but also with increased vascular inflammation and endothelial dysfunction.

Recent epidemiological and genetic evidence has established elevated triglyceride levels and triglyceride-rich lipoproteins as independent contributors to atherosclerotic cardiovascular disease. Large population-based studies and Mendelian randomization analyses have demonstrated that triglyceride-rich lipoprotein remnants are causally associated with ischemic heart disease, supporting their role beyond that of traditional lipid markers [22, 24]. In more contemporary clinical cohorts, elevated triglyceride levels remain associated with residual cardiovascular risk even among patients receiving guideline-directed lipid-lowering therapy. For example, in secondary prevention populations with established cardiovascular disease, higher triglyceride levels have been associated with approximately a 17% increased risk of major cardiovascular events and a 34% higher risk of myocardial infarction, independent of achieved LDL-C levels [25]. These findings reinforce the concept that triglycerides are not only a marker of metabolic dysfunction but an active contributor to atherogenesis and residual cardiovascular risk.

Importantly, dyslipidaemia is closely linked with systemic inflammation and adiposity. Expanded adipose tissue increases the flux of free fatty acids to the liver, promoting hepatic overproduction of VLDL particles and contributing to hypertriglyceridaemia, while inflammatory cytokines further impair lipid metabolism and HDL function [26]. This interaction between lipid abnormalities and inflammation creates a pro-atherogenic environment that accelerates vascular injury and plaque progression.

Taken together, these findings highlight that dyslipidaemia is not merely a disorder of lipid levels but a complex metabolic condition that is closely intertwined with insulin resistance, inflammation, and adiposity. As such, it represents a key component of cardiometabolic risk and an important target for both primary and secondary cardiovascular prevention.

3.3. Inflammation

Although atherosclerotic cardiovascular disease was historically considered primarily a lipid-driven process, currently it is well established that inflammation plays a central role in all stages of atherogenesis, starting with endothelial dysfunction and progressing to plaque rupture and thrombosis [27, 28]. In addition to low-density lipoprotein cholesterol (LDL-C), multiple inflammatory mediators – including high-sensitivity C-reactive protein (hsCRP), interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) – are actively involved in the

initiation and progression of atherosclerosis [29].

C-reactive protein (CRP) is a pentameric acute-phase protein synthesized by hepatocytes in response to cytokine stimulation, particularly IL-6, and serves as a sensitive marker of systemic inflammation [30]. Mechanistically, CRP has been shown to promote endothelial dysfunction by increasing the expression of adhesion molecules, reducing nitric oxide bioavailability, and inducing endothelial cell apoptosis [31]. It may also enhance pro-thrombotic activity by inhibiting fibrinolysis and increasing levels of plasminogen activator inhibitor-1 [32]. Such high-sensitivity assays allow detection of low-grade chronic inflammation, which is particularly relevant in cardiometabolic disease, as elevated hsCRP levels may reflect ongoing inflammatory activity driven by factors such as visceral adiposity, oxidative stress, and endothelial dysfunction [26].

Recent large-scale cohort studies have confirmed the prognostic value of hsCRP in contemporary populations. In a 2025 population-based cohort, individuals with hsCRP ≥2 mg/L had a 22% higher risk of major adverse cardiovascular events, while a concentration of hsCRP >3 mg/L was associated with a 34% higher MACE risk and a 61% increase in cardiovascular mortality compared to levels <1 mg/L, independent of traditional risk factors [7]. Moreover, the data indicate that elevated hsCRP significantly contributes to risk prediction and improves reclassification when added to other established models – for example the integration of hsCRP improved SCORE2 and provided a total net reclassification improvement of 14.1% for prediction of MACE [7].

Notably, inflammation is closely linked to metabolic disorders, including metabolic syndrome and obesity. Adipose tissue, especially when expanded and dysfunctional, becomes infiltrated with macrophages and other immune cells, creating a pro-inflammatory microenvironment characterized by increased secretion of inflammatory cytokines [26]. These adipose tissue-derived inflammatory mediators enter the systemic circulation, where they interfere with insulin signaling, promote endothelial dysfunction, enhance hepatic gluconeogenesis, and contribute to atherosclerotic plaque formation and destabilization [26].

Despite these well-described biological effects, current clinical and genetic evidence suggests that C-reactive protein (CRP) is more likely a marker rather than a causal mediator of atherosclerosis. Mendelian randomization studies have consistently demonstrated that genetically elevated CRP levels are not associated with an increased risk of coronary heart disease, whereas genetic variants affecting interleukin-6 receptor signaling are associated with reduced cardiovascular risk, which supports a causal role for upstream inflammatory pathways [33,34]. Furthermore, although hsCRP is a strong and independent predictor of cardiovascular events in observational studies, interventions that directly target upstream inflammatory mediators – rather than CRP itself – have demonstrated clinical benefit. In the CANTOS trial, inhibition of interleukin-1β reduced major adverse cardiovascular events by approximately 15% (HR 0.85; 95% CI 0.74–0.98), independent of

lipid lowering [35]. These findings support the concept that inflammation plays a causal role in atherosclerosis, while CRP primarily reflects underlying inflammatory activity rather than directly driving progression of the disease.

4. METHODS

The study sample in this retrospective cross-sectional analytical study consisted of men aged 40–55 years and women aged 50–65 years who between 2011 and 2021 participated in the Lithuanian High Cardiovascular Risk Primary Prevention Programme (LitHiR) (hereafter referred to as *the Program*) [36]. The dataset used for statistical analysis was collected from clinical records and routine assessments during the time of 10 years and included a total of 9891 adults (4133 males and 5758 women). The Program offered comprehensive risk assessment and lifestyle counseling to adults who presented for a cardiological consultation, consisting of standardized clinical, anthropometric, biochemical, and vascular evaluations.

Permission No. 2019/3-1104-603 for the biomedical research project *"The Relationship Between Structural and Functional Arterial Changes and Cardiovascular Risk Factors and Events in High-Risk Patients Participating in the Cardiovascular Disease Prevention Program"* was issued by the Vilnius Regional Biomedical Research Ethics Committee. Informed consent was not obtained, as participants were included indirectly and the study was based on retrospective analysis of existing data. All data were anonymized prior to analysis, and individual participants could not be identified. To ensure data quality, only individuals with complete anthropometric and laboratory measurements were included.

4.1. Inclusion Criteria:

A two-level approach, consisting of primary health care institutions and specialized cardiovascular prevention units, was applied to recruit the participants for the study [36]. The inclusion criteria were as follows:

- Women aged 50-64 years and men aged 40-54 years;
- Participants presenting without overt cardiovascular disease.

4.2. Exclusion Criteria:

The exclusion criteria were as follows:

- Clinical manifestation of atherosclerotic cardiovascular disease, including stable or unstable angina pectoris, myocardial infarction, angiographically confirmed coronary atherosclerosis, previous percutaneous coronary intervention, or coronary artery bypass grafting;
- History of cerebrovascular events such as ischemic stroke or transient ischemic attack;
- Clinically evident peripheral arterial disease, including acute ischemic syndromes, chronic limb ischemia, or diagnosed aortic aneurysm;
- Severe comorbidities such as advanced oncologic disease with significant organ failure or

any end-stage systemic illness;

- Advanced heart failure (New York Heart Association class III–IV) or reduced left ventricular systolic function with an ejection fraction below 50%;
- Hemodynamically significant valvular heart disease or cardiac rhythm disorders, including atrial fibrillation, atrial flutter, or frequent ventricular or supraventricular extrasystoles.

4.3. Study Groups

Participants were divided into two groups based on body mass index (BMI), calculated as weight (kg) divided by height squared (m^2). Following World Health Organization (WHO) criteria, individuals with BMI ≥ 30.0 kg/m^2 were classified as obese, while those with BMI < 30.0 kg/m^2 were classified as non-obese. Metabolic syndrome was defined according to the 2005 National Cholesterol Education Programme Adult Treatment Panel III modified criteria [37] and was confirmed when at least three of the following criteria were present:

- Waist circumference ≥ 102 cm in men and ≥ 88 cm in women;
- Serum triglycerides (TG) ≥ 1.7 mmol/l or triglyceride-lowering medication;
- Serum high density lipoprotein cholesterol (HDL-Ch): men < 1.03 mmol/l, women < 1.29 mmol/l or taking lipid-lowering medication;
- Blood pressure: systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg or taking blood pressure lowering medication;
- Fasting glucose ≥ 5.6 mmol/l or diagnosis of DM.

This division was used for all group comparisons. Height and weight were measured by trained staff using calibrated equipment and standardized protocols to ensure consistency.

4.4. Anthropometric and Clinical Measurements

All examinations and measurements were performed during morning hours in a room maintained at a temperature of ≈23 °C. Participants were instructed to arrive after at least 12 hours of fasting, having abstained from alcohol and smoking.

Anthropometric measurements included height, weight, and waist circumference. Waist circumference was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, with the participant standing upright and holding their breath at the end of a normal exhalation.

After at least five minutes of rest in a seated position, arterial blood pressure (BP) was measured on the brachial artery using a manual sphygmomanometer and an appropriately sized cuff for each participant.

4.5. Biochemical Parameters

Venous blood samples were collected in the morning after a 12-hour overnight fast, having

abstained from alcohol and smoking during that period. Serum concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), glucose, high-sensitivity C-reactive protein (hsCRP), and creatinine were measured, along with urinary creatinine and albumin levels.

All biochemical analyses were performed using the ARCHITECT c8000 analyzer (Abbott Laboratories, USA) and corresponding Abbott reagents. The concentration of low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. When triglyceride concentrations exceeded 4.5 mmol/L, LDL-C was measured directly using the same ARCHITECT c8000 analyzer and dedicated Abbott reagents designed for direct LDL determination.

4.6. Echocardiographic Assessment

Participants were examined in the left lateral decubitus position. Standard parasternal and apical views were obtained. Two-dimensional (2D) and M-mode images were acquired during quiet respiration with simultaneous electrocardiographic monitoring. At least three cardiac cycles were recorded for each view.

LV mass was indexed to body surface area (BSA) to account for differences in body size. BSA was calculated using the Mosteller formula: BSA (m^2) = √[(height in cm × weight in kg) / 3,600].

Left ventricular mass index (LVMI) was calculated as: LVMI (g/m^2) = LVM / BSA. Definition of left ventricular hypertrophy (LVH): LVH was defined according to sex-specific cutoffs recommended by the ESC/ESH guidelines [38]: men: LVMI >115 g/m^2, women**:** LVMI >95 g/m^2.

4.7. Statistical Analysis

All statistical analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria; version 4.4.1). Data distribution was assessed visually using histograms, and variables showing an approximately bell-shaped distribution were considered normally distributed. Continuous variables are presented as mean ± standard deviation (SD) for approximately normally distributed data and as median with interquartile range (IQR) for non-normally distributed data, while categorical variables are expressed as counts and percentages.

Multivariable regression models were adjusted for clinically relevant covariates, including age, sex, measures of adiposity, blood pressure, smoking status, and metabolic parameters, as appropriate for each outcome. In selected models, body mass index (BMI) and waist circumference were included simultaneously to distinguish the effects of overall adiposity from central fat distribution. Multicollinearity was evaluated using variance inflation factors (VIF), with no evidence of problematic collinearity observed (VIF < 3). Sensitivity analyses were performed using alternative model specifications to assess the robustness of the findings.

Effect modification was explored by introducing interaction terms between inflammatory markers and adiposity-related variables. Model adequacy and parsimony were evaluated using standard

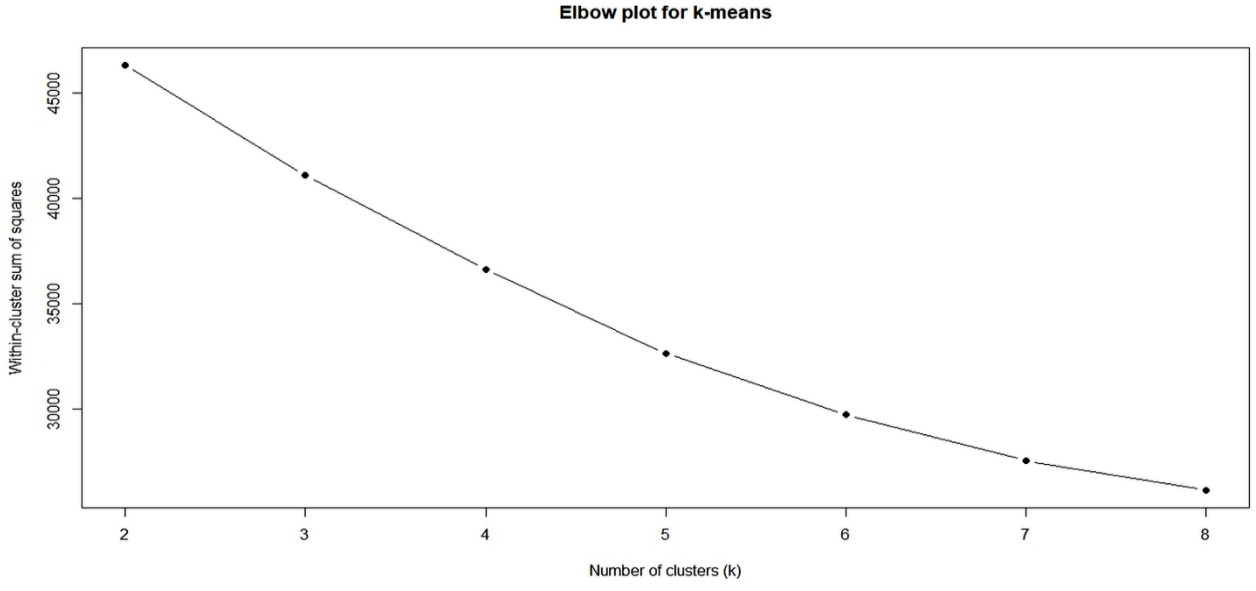
information criteria. To assess potential non-linear associations, restricted cubic spline regression with three degrees of freedom was applied to log-transformed C-reactive protein (CRP). Spline models were compared with corresponding linear models to evaluate improvements in model fit.

The discriminative ability of selected logistic regression models was evaluated using receiver operating characteristic (ROC) curve analysis. Area under the curve (AUC) values with 95% confidence intervals were estimated, and comparisons between models were performed using DeLong's test.

Mediation analysis was conducted to examine potential indirect effects through intermediate variables, within a counterfactual framework. Indirect, direct, and total effects were estimated using nonparametric bootstrap resampling with 1,000 iterations.

Unsupervised k-means clustering was applied to identify cardiometabolic phenotypes based on selected anthropometric, metabolic, and inflammatory variables. Prior to clustering, all variables were standardized to z-scores (mean=0, SD=1) to ensure equal weighting. The optimal number of clusters (k) was determined by examining the within-cluster sum of squares (WSS) as a function of k (elbow method), the silhouette coefficient and clustering robustness was supported by multiple random initializations (*Figure 1*). Identified clusters were subsequently characterized by comparing standardized variable profiles. Continuous variables were compared across clusters using one-way ANOVA followed by Tukey's post-hoc test. Categorical outcomes were compared using χ^2 tests with Holm-adjusted pairwise proportion tests. Groups sharing the same symbol in post-hoc comparisons were not statistically different. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Figure 1 *Elbow plot for k-means. Elbow plot showing within-cluster sum of squares across increasing numbers of clusters (k). The inflection point suggests the optimal number of clusters used for k-means clustering analysis.*



5. RESULTS

5.1. Descriptive Comparison

Table 1 summarizes the profile of study participants. When comparing anthropometric and biochemical characteristics, waist circumference and both systolic and diastolic blood pressure were significantly higher in obese participants than in non-obese individuals. Analysis of metabolic parameters showed that triglyceride levels and fasting glucose were modestly but significantly higher in the obese group, while HDL-cholesterol levels were lower. In contrast, mean LDL-cholesterol and total cholesterol were slightly but significantly lower among obese participants. In addition, hsCRP concentrations were significantly elevated in obese individuals compared with non-obese participants ($p < 0.001$), indicating the presence of low-grade systemic inflammation associated with increased adiposity. Overall, obese participants exhibited a more adverse metabolic profile characterized by greater central adiposity, higher blood pressure, elevated triglycerides, higher fasting glucose, lower HDL-cholesterol, and increased inflammatory markers

Table 1. *Comparative Clinical and Biochemical Characteristics of Obese and Non-Obese Participants*

Variable	**All participants (n = 9,891) Mean ± SD**	**Non-obese (n = 3,804) Mean ± SD**	**Obese (n = 6,087) Mean ± SD**	**p value**
Anthropometric data				
Sex, n (%)	Male 4,133 (41.8%) Female 5,758 (58.2%)	Male 1,594 (41.9%) Female 2,210 (58.1%)	Male 2,539 (41.7%) Female 3,548 (58.3%)	0.93[b]
Age, years	53.5 ± 6.5	52.9 ± 6.4	53.8 ± 6.5	0.002
BMI, kg/m²	31.2 ± 5.8	27.7 ± 2.8	33.4 ± 4.3	< 0.001
Waist circumference[a], cm	104.3 ± 11.6	94.6 ± 8.3	110.1 ± 9.7	< 0.001
Systolic BP[a], mmHg	137.8 ± 15.4	134.6 ± 14.8	139.8 ± 15.5	< 0.001
Diastolic BP[a], mmHg	83.3 ± 10.7	82.4 ± 10.5	83.9 ± 10.8	< 0.001
Biochemical parameters				
Total cholesterol[a], mmol/L	6.24 ± 1.36	6.34 ± 1.39	6.17 ± 1.34	< 0.001

Table 1. *Comparative Clinical and Biochemical Characteristics of Obese and Non-Obese Participants* (Continuation)

LDL-cholesterol[a], mmol/L	3.10 ± 0.91	3.16 ± 0.89	3.06 ± 0.92	0.009
HDL-cholesterol[a], mmol/L	1.28 ± 0.33	1.40 ± 0.33	1.21 ± 0.31	< 0.001
Triglycerides, mmol/L	1.36 ± 0.75	1.23 ± 0.65	1.44 ± 0.79	< 0.001
Fasting glucose, mmol/L	6.28 ± 1.21	6.21 ± 1.19	6.32 ± 1.22	0.012
hsCRP, mg/L	2.30 ± 1.98	1.77 ± 1.77	2.65 ± 1.97	< 0.001
Creatinine[a], µmol/L	77.6 ± 17.5	74.8 ± 16.2	79.4 ± 18.1	< 0.001

[a]*: Normal distribution*

[b]*: Chi-square test*

Abbreviations: BMI – body mass index; BP – blood pressure; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; hsCRP – high-sensitivity C-reactive protein.

5.2. Systemic Inflammation and Glucose Metabolism

5.2.1. hsCRP Levels According to Obesity Status

As seen in table 1, hsCRP concentrations differed significantly according to obesity status with obese participants exhibiting higher mean hsCRP levels when compared with non-obese individuals (2.65 ± 1.97 mg/L vs. 1.77 ± 1.77 mg/L, $p < 0.001$). The distribution of hsCRP values was right skewed in both groups, with a higher proportion of elevated values among obese participants (*Figure 2*). Because hsCRP values were right-skewed, CRP was log-transformed for all regression analyses.

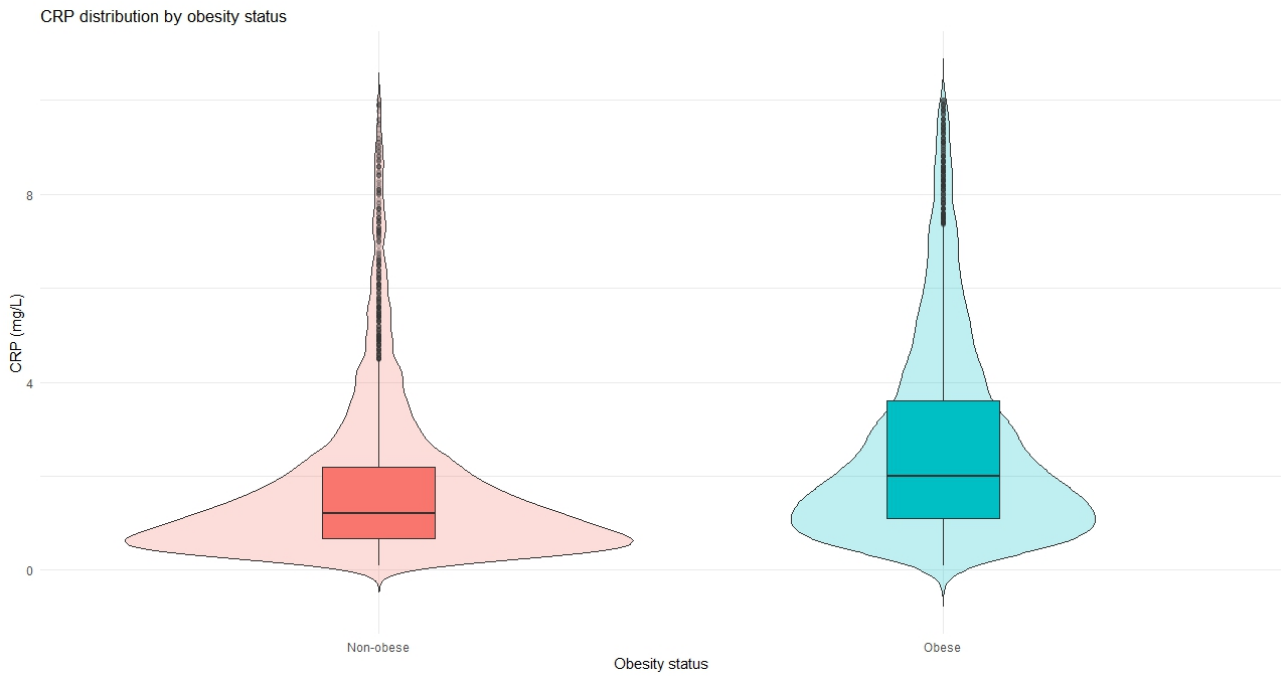


Figure 2. *Distribution of C-reactive protein (CRP) levels by obesity status. Violin plots with embedded boxplots show CRP concentrations (mg/L) in non-obese and obese groups. The central line represents the median, and the boxes indicate the interquartile range.*

5.2.2. Correlation Analysis

Spearman correlation analyses were performed to explore relationships between inflammatory, anthropometric, and metabolic variables in the overall cohort and after stratification by obesity status (*Table 2-4; Figure 3-5*). In the overall cohort, hsCRP showed positive correlations with BMI ($\rho = 0.326$), waist circumference ($\rho = 0.257$), fasting glucose ($\rho = 0.087$), and triglycerides ($\rho = 0.073$), while a weak inverse correlation was observed with HDL-cholesterol ($\rho = -0.052$) (all $p < 0.001$). Strong relationships were observed between BMI and waist circumference and between triglycerides and HDL-cholesterol, reflecting typical metabolic syndrome patterns.

When stratified by obesity status, the association between hsCRP and fasting glucose differed between groups. Among obese participants, hsCRP was positively correlated with fasting glucose ($\rho = 0.082$, $p < 0.001$), whereas no significant association was observed among non-obese individuals. In both groups, hsCRP remained positively correlated with measures of adiposity, including BMI and waist circumference. Additionally, triglycerides demonstrated a consistent moderate inverse correlation with HDL-cholesterol in both obese and non-obese participants, indicating a similar dyslipidaemic pattern across BMI categories.

Overall, these findings suggest that systemic inflammation is more strongly linked to glycaemic dysregulation in obese individuals, while associations between adiposity and inflammatory markers were present across both groups.

Table 2. *Spearman correlations between cardiometabolic variables in the overall cohort (n =*

9,891)

Variable	hsCRP	HDL	Fasting glucose	Waist circumference	BMI	Triglycerides
hsCRP	1.000	-0.052	0.087	0.257	0.326	0.073
HDL	-0.052	1.000	-0.034	-0.281	-0.145	-0.419
Fasting glucose	0.087	-0.034	1.000	0.152	0.170	0.084
Waist circumference	0.257	-0.281	0.152	1.000	0.704	0.162
BMI	0.326	-0.145	0.170	0.704	1.000	0.089
Triglycerides	0.073	-0.419	0.084	0.162	0.089	1.000

All correlations $p < 0.001$ except HDL–glucose ($p = 0.0009$).

Abbreviations: BMI – body mass index; HDL-C – high-density lipoprotein cholesterol; hsCRP – high-sensitivity C-reactive protein.

	hsCRP	HDL	FG	WC	BMI	TG
hsCRP	1	-0.05	0.09	0.26	0.33	0.07
HDL	-0.05	1	-0.03	-0.28	-0.15	-0.42
FG	0.09	-0.03	1	0.15	0.17	0.08
WC	0.26	-0.28	0.15	1	0.70	0.16
BMI	0.33	-0.15	0.17	0.70	1	0.09
TG	0.07	-0.42	0.08	0.16	0.09	1

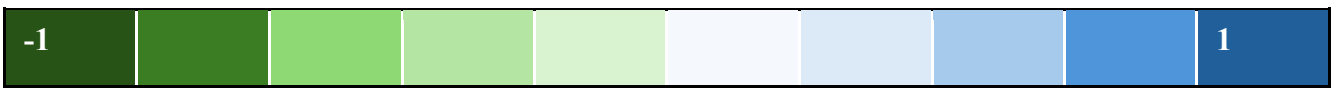


Figure 3. *Correlation matrix of cardiometabolic variables in the overall study population. Heatmap showing pairwise correlations between high-sensitivity C-reactive protein (hsCRP), high-density lipoprotein cholesterol (HDL), fasting glucose (FG), waist circumference (WC), body mass index (BMI), and triglycerides (TG) in the full cohort. Color intensity represents the strength and direction of correlations, ranging from negative (green) to positive (blue), with darker shades indicating stronger associations. Values within cells represent correlation coefficients.*

Table 3. *Spearman correlations in obese participants (n = 6,087)*

Variable	hsCRP	HDL	Fasting glucose	Waist circumference	BMI	Triglycerides
hsCRP	1.000	0.018	0.082	0.147	0.234	0.042
HDL	0.018	1.000	-0.033	-0.241	-0.028	-0.409
Fasting glucose	0.082	-0.033	1.000	0.122	0.136	0.093
Waist circumference	0.147	-0.241	0.122	1.000	0.518	0.148
BMI	0.234	-0.028	0.136	0.518	1.000	0.033
Triglycerides	0.042	-0.409	0.093	0.148	0.033	1.000

All correlations $p < 0.001$ except CRP–HDL ($p = 0.168$); CRP–triglycerides ($p = 0.001$); HDL–fasting glucose ($p = 0.010$); HDL–BMI ($p = 0.029$); BMI–triglycerides ($p = 0.011$).

Abbreviations: BMI – body mass index; HDL-C – high-density lipoprotein cholesterol; hsCRP – high-sensitivity C-reactive protein.

Variable	hsCRP	HDL	FG	WC	BMI	TG
hsCRP	1.000	0.018	0.082	0.147	0.234	0.042
HDL	0.018	1.000	-0.033	-0.241	-0.028	-0.409
FG	0.082	-0.033	1.000	0.122	0.136	0.093
WC	0.147	-0.241	0.122	1.000	0.518	0.148
BMI	0.234	-0.028	0.136	0.518	1.000	0.033
TG	0.042	-0.409	0.093	0.148	0.033	1.000

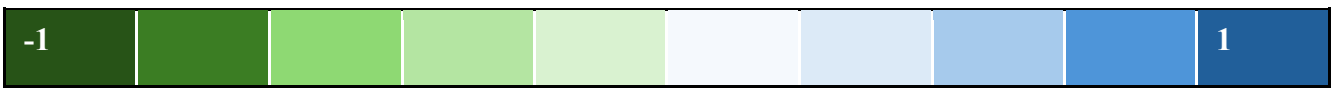


Figure 4. *Correlation matrix of cardiometabolic variables in obese participants. Heatmap showing pairwise correlations between high-sensitivity C-reactive protein (hsCRP), high-density lipoprotein cholesterol (HDL), fasting glucose (FG), waist circumference (WC), body mass index (BMI), and triglycerides (TG) in the obese group. Color intensity represents the strength and direction of correlations, ranging from negative (green) to positive (blue), with darker shades indicating stronger associations. Values within cells represent correlation coefficients.*

Table 4. *Spearman correlations in non-obese participants (n = 3,804)*

Variable	hsCRP	HDL	Fasting glucose	Waist circumference	BMI	Triglycerides
hsCRP	1.000	-0.077	0.017	0.143	0.175	0.085
HDL	-0.077	1.000	0.008	-0.273	-0.145	-0.425
Fasting glucose	0.017	0.008	1.000	0.044	0.061	0.048
Waist circumference	0.143	-0.273	0.044	1.000	0.499	0.149
BMI	0.175	-0.145	0.061	0.499	1.000	0.102
Triglycerides	0.085	-0.425	0.048	0.149	0.102	1.000

All correlations $p < 0.001$ except CRP–fasting glucose ($p = 0.306$); HDL–fasting glucose ($p = 0.638$); fasting glucose–waist circumference ($p = 0.006$); fasting glucose–triglycerides ($p = 0.003$). Abbreviations: BMI – body mass index; HDL-C – high-density lipoprotein cholesterol; hsCRP – high-sensitivity C-reactive protein.

Variable	hsCRP	HDL	FG	WC	BMI	TG
hsCRP	1.000	-0.077	0.017	0.143	0.175	0.085
HDL	-0.077	1.000	0.008	-0.273	-0.145	-0.425
FG	0.017	0.008	1.000	0.044	0.061	0.048
WC	0.143	-0.273	0.044	1.000	0.499	0.149
BMI	0.175	-0.145	0.061	0.499	1.000	0.102
TG	0.085	-0.425	0.048	0.149	0.102	1.000

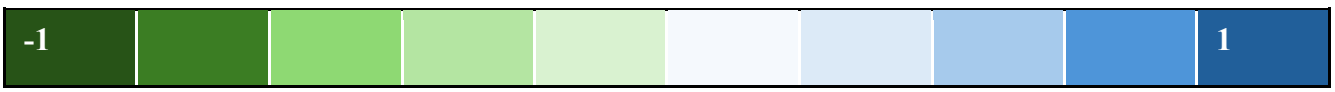


Figure 5. *Correlation matrix of cardiometabolic variables in non-obese participants. Heatmap showing pairwise correlations between high-sensitivity C-reactive protein (hsCRP), high-density lipoprotein cholesterol (HDL), fasting glucose(FG), waist circumference (WC), body mass index (BMI), and triglycerides (TG) in the non-obese group. Color intensity represents the strength and direction of correlations, ranging from negative (green) to positive (blue), with darker shades indicating stronger associations. Values within cells represent correlation coefficients.*

5.2.3. Association Between hsCRP and Fasting Glucose

During further analysis we observed how higher hsCRP levels were associated with higher fasting glucose concentrations in the overall cohort: log-transformed hsCRP remained an independent predictor of fasting glucose and when stratified by obesity status, the association between inflammation and glucose regulation differed markedly between the two groups. As shown in table 5, among the obese participants, log(hsCRP) was strongly and independently associated with fasting glucose, while no statistically significant association was observed in the non-obese subgroup. After introducing a formal interaction term, a significant modifying effect of obesity on the hsCRP – glucose relationship was observed, confirming that the metabolic impact of inflammation was substantially stronger in obese individuals (*Figure 6*).

Table 5. *Multivariable Linear Regression Models for Fasting Glucose According to hsCRP and Obesity Status.*

Model / Variable	**β coefficient**	**Standard Error**	**p-value**
Overall cohort (n = 9,891)			
log(hsCRP)	0.068	0.016	< 0.001
Age (years)	0.018	0.003	< 0.001
Waist circumference (cm)	0.006	0.002	0.001
BMI (kg/m²)	0.026	0.004	< 0.001
Male sex	0.216	0.039	< 0.001
Obese participants (BMI ≥ 30 kg/m²)			
log(hsCRP)	0.105	0.022	< 0.001
Non-obese participants (BMI < 30 kg/m²)			
log(hsCRP)	0.017	0.022	0.44
Interaction model			
log(hsCRP) × Obesity	0.126	0.032	< 0.001

Models adjusted for age, sex, BMI, and waist circumference (where applicable). β coefficients represent the change in fasting glucose (mmol/L) per one-unit increase in log-transformed hsCRP.

β coefficient, regression coefficient; BMI, body mass index; log(hsCRP), log-transformed high-sensitivity C-reactive protein.

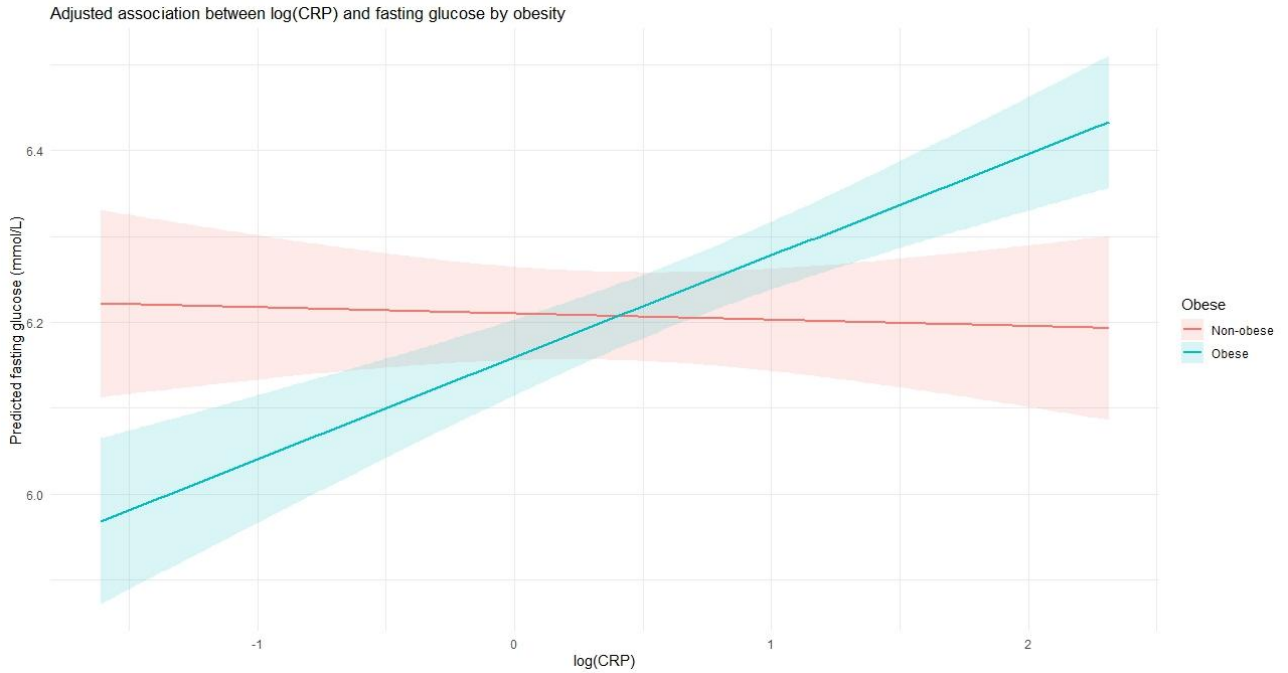


Figure 6. *Adjusted association between log-transformed C-reactive protein (CRP) and fasting glucose by obesity status. Predicted fasting glucose levels (mmol/L) across log-transformed CRP are shown separately for non-obese and obese groups based on multivariable-adjusted models. Shaded areas represent 95% confidence intervals.*

To explore potential non-linear relationships, we applied a spline regression with three degrees of freedom, which, when compared with a linear model, demonstrated a significantly improved fit ($p < 0.001$). The adjusted association between hsCRP and fasting glucose was relatively flat at lower hsCRP concentrations but increased steeply beyond 2–3 mg/L, indicating a non-linear, threshold-type relationship (*Figure 7*).

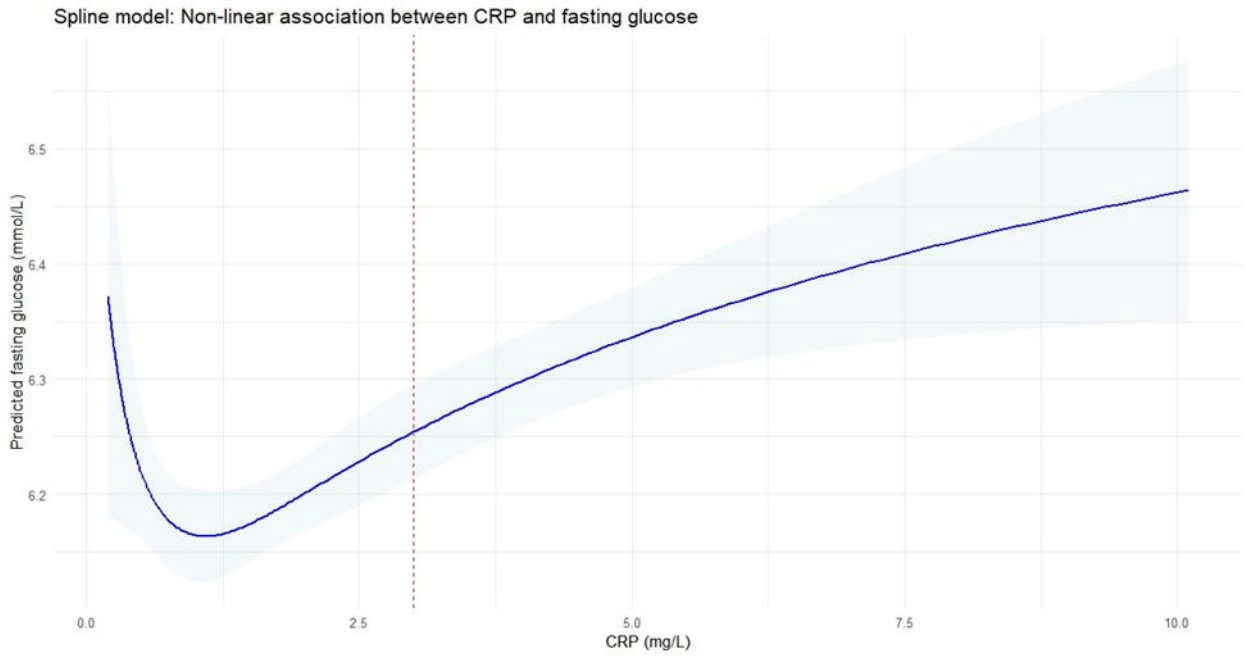


Figure 7. *Spline curve: non-linear hsCRP–glucose relationship. Restricted cubic spline analysis demonstrating the relationship between log-transformed high-sensitivity C-reactive protein (hsCRP) and predicted fasting glucose levels. The solid line represents the adjusted association, and the shaded area indicates the 95% confidence interval. The relationship shows a non-linear, threshold-type pattern, with relatively stable glucose levels at lower hsCRP concentrations and a steeper increase beyond approximately 2–3 mg/L (dashed vertical line). Models were adjusted for age, sex, body mass index, and waist circumference.*

5.3. Metabolic Syndrome and Cardiometabolic Phenotypes

5.3.1. Prevalence of Metabolic Abnormalities by Obesity Status

Given the strong interaction between systemic inflammation and adiposity in relation to glucose regulation, we next examined the prevalence and determinants of clinically defined metabolic abnormalities across the cohort (*Table 6*). Although obesity was associated with a higher prevalence of all metabolic abnormalities, the persistently high prevalence of metabolic syndrome and its complications in non-obese individuals signaled that cardiometabolic risk was not only confined to obesity, nevertheless these findings should be interpreted in the context of the study population, which represents a higher-risk cohort rather than the general population.

Table 6. *Prevalence of metabolic abnormalities among non-obese and obese adults (n = 9,891)*

Variable	**Non-Obese (n = 3,804)**	**Obese (n = 6,087)**	**p-value**
Metabolic Syndrome	2,898 (76.2%)	5,462 (89.7%)	<0.001
Hypertension	3,256 (85.6%)	5,732 (94.2%)	<0.001
Left Ventricular Hypertrophy	1,463 (38.5%)	2,996 (49.2%)	<0.001

Table 6. *Prevalence of metabolic abnormalities among non-obese and obese adults (n = 9,891)* (Continuation)

Diabetes	503 (13.2%)	1,236 (20.3%)	<0.001

5.3.2. Multivariable Predictors of Metabolic Syndrome

As presented in table 7, BMI, waist circumference, triglyceride concentration, hsCRP, age, and sex were all independently associated with the presence of metabolic syndrome. Notably, among these variables, as expected given their inclusion in the diagnostic criteria, triglycerides emerged as the strongest predictor, with each 1 mmol/L increase associated with nearly a fourfold higher odds of metabolic syndrome.

Table 7. *Multivariable Logistic Regression for Predictors of Metabolic Syndrome*

Variable	Odds Ratio (OR)	95% CI	p-value
BMI (kg/m²)	1.06	1.04 – 1.09	<0.001
Waist circumference (cm)	1.05	1.04 – 1.06	<0.001
Triglycerides (mmol/L)	3.81	3.43 – 4.25	<0.001
log(CRP)	1.12	1.04 – 1.21	0.005
Age (years)	1.05	1.03 – 1.06	<0.001
Sex (male)	0.79	0.64 – 0.96	0.018

Model statistics: AIC = 6915; McFadden's pseudo-R^2 = 0.19.
All variables included simultaneously in the model. Odds ratios are mutually adjusted for all variables shown in the table.
BMI, body mass index; log(hsCRP), log-transformed high-sensitivity C-reactive protein.

Further interaction effects were observed between adiposity measures and inflammation, in particular, the association between hsCRP and metabolic syndrome was modified by BMI (BMI × hsCRP interaction p = 0.018), with the steepest increase in metabolic syndrome probability observed among individuals with moderate BMI values (*Figure 8*).

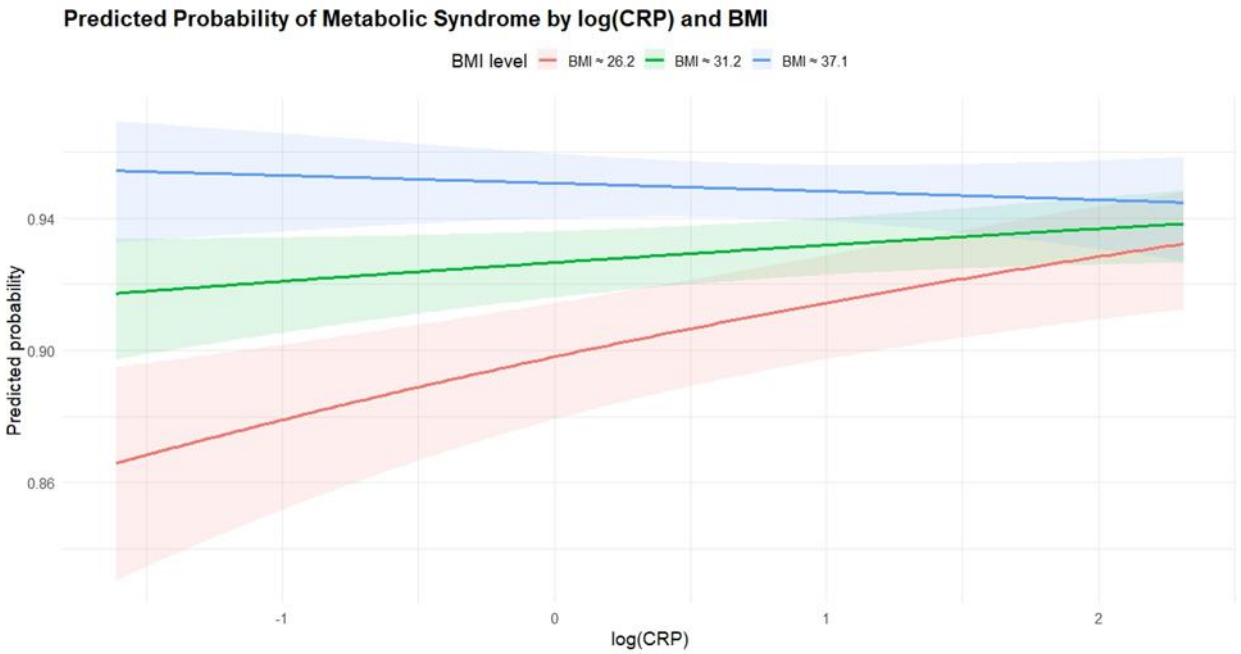


Figure 8. *Predicted probability of metabolic syndrome by log-transformed CRP across BMI levels. Predicted probability of metabolic syndrome derived from multivariable logistic regression models across increasing levels of log-transformed high-sensitivity C-reactive protein (hsCRP), stratified by body mass index (BMI). Lines represent estimated probabilities at representative BMI levels (26.2, 31.2, and 37.1 kg/m²), and shaded areas indicate 95% confidence intervals. The association between hsCRP and metabolic syndrome probability varies across BMI levels, demonstrating a significant interaction between systemic inflammation and adiposity, with a steeper increase in predicted risk at lower to moderate BMI levels.*

5.3.3. Cardiometabolic Phenotypes Identified by Cluster Analysis

Unsupervised k-means clustering based on BMI, waist circumference, fasting glucose, triglycerides, HDL cholesterol, and log-transformed CRP identified four distinct cardiometabolic phenotypes within our cohort (*Figure 9-10*):

1. Diabetic-obese phenotype: high BMI and waist circumference with markedly elevated glucose;
2. Obese-dyslipidemic phenotype: very high adiposity accompanied by high triglycerides, low HDL-C, and elevated hsCRP;
3. Metabolically healthy non-obese phenotype: moderate BMI, low hsCRP, and favorable lipid levels;
4. Inflamed high-triglyceride phenotype: only moderate BMI yet disproportionately high triglycerides, elevated hsCRP, and low HDL-C.

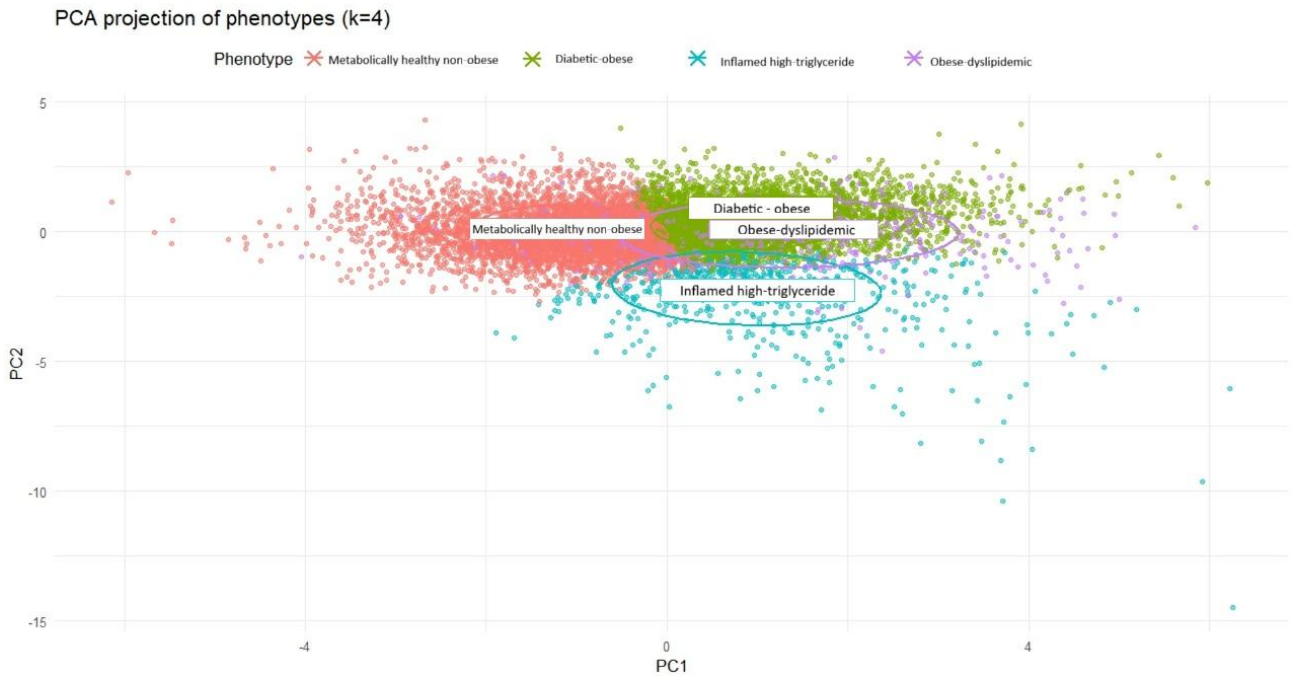


Figure 9. *Principal component analysis (PCA) projection of cardiometabolic phenotypes (k = 4). Two-dimensional PCA projection of participants according to cardiometabolic phenotype identified by k-means clustering (k = 4), including metabolically healthy non-obese, diabetic-obese, obese-dyslipidemic, and inflamed high-triglyceride subgroups. Each point represents an individual, and colors indicate cluster assignment. Ellipses represent cluster dispersion in the PCA space*.

Despite similar levels of adiposity, individuals in the inflamed high-triglyceride phenotype demonstrated substantially greater metabolic derangements than those in the metabolically healthy non-obese phenotype, which indicated that inflammation and dyslipidaemia may contribute to metabolic risk beyond overall adiposity (*Table 8*).

Table 8. *Cardiometabolic Characteristics Across Phenotypes Identified by k-Means Clustering*

Variable	**Diabetic–Obese (n=418, 4.2%)**	**Obese–Dyslipidemic (n=4157, 42.0%)**	**Metabolically Healthy Non-Obese (n=4721, 47.7%)**	**Inflamed High-TG (n=595, 6.0%)**	**p-value**	**Post-hoc**
BMI (kg/m²)	33.0 ± 4.3	34.6 ± 3.5	28.6 ± 2.8	31.1 ± 3.5	<0.001	2 > 1 > 4 > 3
Waist circumference (cm)	108.0 ± 10.8	111.3 ± 8.3	97.0 ± 7.2	105.8 ± 9.0	<0.001	2 > 1 > 4 > 3

Table 8. *Cardiometabolic Characteristics Across Phenotypes Identified by k-Means Clustering.* (Continuation)

Fasting glucose (mmol/L)	10.44 ± 2.54	6.14 ± 0.76	5.94 ± 0.71	6.29 ± 0.84	<0.001	1 > 4 > 2 > 3
TG (mmol/L)	2.40 ± 1.32	1.96 ± 1.01	1.70 ± 0.90	6.25 ± 3.60	<0.001	4 > 1 > 2 > 3
HDL (mmol/L)	1.18 ± 0.33	1.16 ± 0.29	1.34 ± 0.31	0.92 ± 0.27	<0.001	3 > (1 = 2) > 4
hsCRP (mg/L)	2.25 ± 2.05	2.64 ± 2.25	1.24 ± 1.74	1.70 ± 1.94	<0.001	2 > 1 > 4 > 3
Age (years)	53.8 ± 6.1	53.0 ± 6.5	54.3 ± 6.4	49.5 ± 5.7	<0.001	3 > 1 > 2 > 4
Systolic BP (mmHg)	142.1 ± 16.9	139.3 ± 15.5	134.3 ± 14.7	139.4 ± 15.0	<0.001	1 > 4 = 2 > 3
Diastolic BP (mmHg)	84.9 ± 10.4	83.6 ± 10.7	81.7 ± 10.3	87.1 ± 10.8	<0.001	4 > 1 = 2 > 3
Total cholesterol (mmol/L)	5.8 ± 1.4	6.0 ± 1.3	6.3 ± 1.4	7.0 ± 1.6	<0.001	4 > 3 > 2 > 1
LDL (mmol/L)	3.5 ± 1.2	3.9 ± 1.1	4.2 ± 1.2	3.3 ± 1.1	<0.001	3 > 2 > 1 > 4
Metabolic syndrome, n (%)	399 (95.5%)	3813 (91.7%)	3568 (75.6%)	580 (97.5%)	<0.001	4 = 1 > 2 > 3
Hypertension, n (%)	401 (95.9%)	3924 (94.4%)	4124 (87.4%)	539 (90.6%)	<0.001	1 = 2 > 4 = 3
Diabetes, n (%)	363 (86.8%)	720 (17.3%)	547 (11.6%)	109 (18.3%)	<0.001	1 > 4 = 2 > 3
LVH, n (%)	212 (50.7%)	2101 (50.5%)	1863 (39.5%)	283 (47.6%)	<0.001	1 = 2 = 4 > 3

One-way ANOVA with Tukey post-hoc test was used for continuous variables; χ^2 tests with Holm-adjusted pairwise comparisons for categorical variables. Identical symbols indicate no significant

difference.

BMI, body mass index; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; LVH, left ventricular hypertrophy.

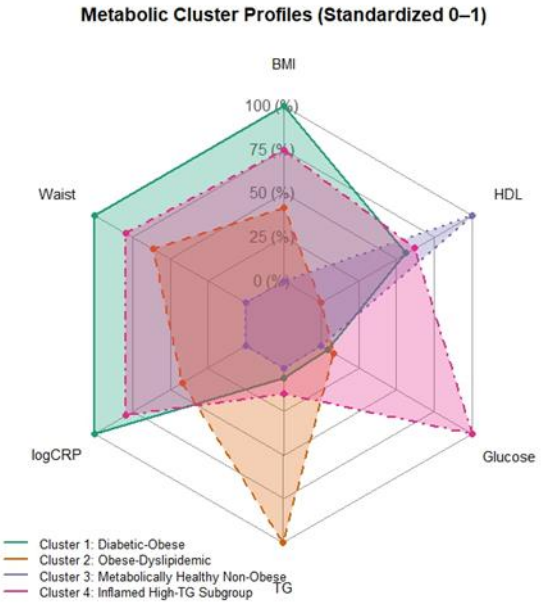


Figure 10. *Metabolic Cluster Profiles. Radar plot illustrating standardized profiles of cardiometabolic variables across four clusters identified using k-means clustering: diabetic-obese, obese-dyslipidemic, metabolically healthy non-obese, and inflamed high-triglyceride phenotypes. Variables include body mass index (BMI), waist circumference, high-density lipoprotein cholesterol (HDL-C), fasting glucose, triglycerides (TG), and log-transformed high-sensitivity C-reactive protein (hsCRP). Values are presented as normalized percentages to facilitate comparison across variables. The clusters demonstrate distinct metabolic and inflammatory patterns, highlighting heterogeneity in cardiometabolic risk beyond BMI classification.*

5.4. Structural Cardiac Remodeling: Left Ventricular Hypertrophy

5.4.1. Prevalence of Left Ventricular Hypertrophy

During further analysis, our study demonstrated that ventricular hypertrophy was highly prevalent among the participants, affecting 45.1% in total, with LVH being significantly more common among obese individuals (*Table 9*). Alarmingly, despite lower overall adiposity, more than one-third of the non-obese adults also exhibited LVH.

Table 9. *Prevalence and clinical correlates of left ventricular hypertrophy (LVH)*

Variable	**LVH Present (%)**	**LVH Absent (%)**	**p-value**
Overall prevalence	45.1%	54.9%	—
By obesity status			

Table 9. *Prevalence and clinical correlates of left ventricular hypertrophy (LVH)* (Continuation)

Non-obese	38.5%	61.5%	< 0.001
Obese	49.2%	50.8%	
Waist circumference (cm, mean ± SD)	105.3 ± 11.7	103.0 ± 11.3	< 0.001
Hypertension			
Normotensive	5.9%	94.1%	< 0.001
Hypertensive	49.0%	51.0%	

SD, standard deviation; LVH, left ventricular hypertrophy.

5.4.2. Multivariable Predictors of Left Ventricular Hypertrophy

In our study several factors emerged as independent predictors of LVH: higher BMI, larger waist circumference, elevated systolic blood pressure, older age, and smoking were all significantly associated with the increased odds of LVH and when stratified by obesity status the pattern of LVH predictors remained largely consistent across groups (*Table 10*).

However, our analysis did not find hsCRP and fasting glucose to be independently associated with LVH after adjustment and stratification by obesity status, indicating that inflammatory and glycaemic factors most likely did not exert a direct effect on structural cardiac remodeling beyond adiposity and hemodynamic influences.

Table 10. *Multivariable logistic regression models identifying predictors of left ventricular hypertrophy (LVH)*

Predictor	**Overall cohort OR (95% CI)**	**p-value**	**Non-obese OR (p-value)**	**Obese OR (p-value)**
BMI (kg/m²)	1.04 (1.02–1.05)	<0.001	—	—
Waist circumference (cm)	1.01 (1.01–1.02)	<0.001	1.02 (<0.001)	1.02 (<0.001)
Systolic BP (mmHg)	1.01 (1.01–1.02)	<0.001	1.02 (<0.001)	1.01 (<0.001)
log(hsCRP)	1.02 (0.97–1.08)	0.40	1.02 (0.74)	1.05 (0.19)
Fasting glucose (mmol/L)	1.03 (0.99–1.06)	0.15	1.04 (0.25)	1.03 (0.22)
Smoking (yes vs no)	1.21 (1.10–1.33)	<0.001	1.19 (0.03)	1.21 (0.003)
Age (years)	1.03 (1.02–1.04)	<0.001	1.04 (<0.001)	1.03 (<0.001)
Sex (male)	0.94 (0.82–1.07)	0.35	0.96 (0.72)	0.83 (0.02)

Overall model fit: AIC = 13,219; McFadden pseudo-R^2 = 0.03. Models adjusted for: age, sex, BMI, waist circumference, systolic blood pressure, smoking status, hsCRP, and fasting glucose Stratified models: Both models significant (p < 0.001)

Collinearity: All variance inflation factors (VIF) < 2.8.

OR, odds ratio; CI, confidence interval; BMI, body mass index; BP, blood pressure; hsCRP, high-sensitivity C-reactive protein; AIC, Akaike Information Criterion; VIF, variance inflation factor.

5.4.3. Mediation Analysis: Role of Hypertension

To conclude the analysis, we lastly assessed whether hypertension mediated the relationship between central adiposity and LVH using waist circumference as the exposure, hypertension as the mediator, and LVH as the outcome. Our findings suggest that hypertension accounted for approximately 7.4% of the total association between waist circumference and LVH (p = 0.002), therefore, the direct effect of waist circumference on LVH remained statistically significant, indicating partial mediation (*Figure 11*).

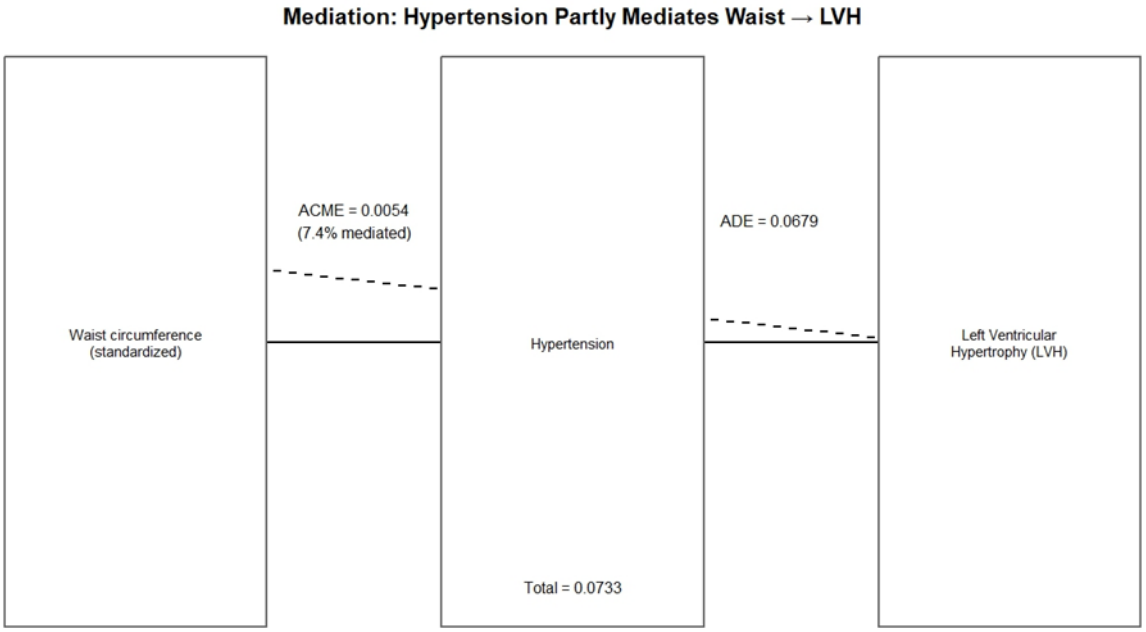


Figure 11. *Hypertension partially mediates the association between waist circumference and LVH. Diagram illustrating the mediation model assessing the role of hypertension in the association between standardized waist circumference and left ventricular hypertrophy (LVH). The total effect of waist circumference on LVH is decomposed into a direct effect (average direct effect [ADE] = 0.0679) and an indirect effect mediated through hypertension (average causal mediation effect [ACME] = 0.0054), corresponding to 7.4% of the total effect. The direct pathway remained statistically significant, indicating partial mediation and suggesting that central adiposity contributes to cardiac remodeling both through blood pressure–mediated mechanisms and additional pathways independent of hypertension.*

6. DISCUSSION

6.1. Overview

In this large cohort of 9891 obese and non-obese participants we observed clear anthropometric and

biochemical differences between the groups. While no major differences were observed in levels of total and LDL cholesterol, obese participants showed significantly lower HDL cholesterol and higher waist circumference, blood pressure, fasting glucose, triglycerides and hsCRP. Notably, hsCRP was independently associated with fasting glucose, with a markedly stronger effect in obese participants and no significant association in the non-obese subgroup, which suggests that excess adiposity does amplify the metabolic consequences of inflammation. In addition to these findings, we observed a significantly larger prevalence of cardiological risk factors among the obese participants, which highlights how excess adiposity amplifies inflammatory and glycemic disturbances, which in turn results in metabolic dysregulation and cardiovascular events. Importantly, an alarming rate of early metabolic and inflammatory changes were also seen in the non-obese group, which strongly supports the "metabolically unhealthy normal-weight" phenotype and underscores how metabolic risk extends beyond BMI-defined obesity.

6.2. Systemic Inflammation and Glucose Metabolism

Our findings that CRP correlated positively with fasting glucose and triglycerides, and negatively with HDL-C in both BMI groups, follow the growing evidence linking low-grade systemic inflammation to insulin resistance, dyslipidaemia, and metabolic syndrome. A large study by Huihui Sun and co – authors aimed to explore the association between the hs-CRP/HDL-C ratio and the presence of prediabetes and diabetes demonstrated that elevated hs-CRP independently predicts incident type 2 diabetes, even when adjusted for BMI, waist circumference and other risk factors [39]. Thus, CRP is increasingly recognized not only as a result of metabolic disturbance but as an active contributor to metabolic dysfunction.

It's important to note that in our multivariable regression models, log-transformed hsCRP remained an independent predictor of fasting glucose in the overall cohort, with a markedly stronger association observed among obese participants. In contrast, this relationship was attenuated and not statistically significant in the non-obese subgroup, which indicates that excess adiposity amplifies the metabolic impact of systemic inflammation. Although our findings suggest that CRP-driven dysglycaemia becomes clinically relevant primarily in the presence of obesity or increased adiposity, several previous studies have shown that even among individuals with normal BMI, elevated CRP levels are associated with increased cardiometabolic risk, which supports the concept that inflammation may drive metabolic disturbance even in individuals with "normal" BMI, more specifically - the metabolically unhealthy normal-weight (MUNW) phenotype. Previous analysis had shown that even among individuals with normal BMI but elevated CRP, there was an increased cardiometabolic risk: for example, large prospective cohorts have shown that circulating CRP discriminates cardiometabolic risk within BMI strata, identifying higher-risk individuals despite similar BMI - a finding exemplified by the van Wijk et al. analysis, which showed CRP

differentiates lower- and higher-risk “metabolically healthy” phenotypes independent of BMI [40]. In this context, our findings further add evidence by demonstrating that inflammation interacts with adiposity to drive glucose dysregulation, rather than exerting uniform metabolic effects across BMI categories.

6.3. Cardiovascular Risk Factors

We recorded a high prevalence of hypertension (90,9%) and left ventricular hypertrophy (45,1%) in our study, and it is consistent with prior epidemiological data linking obesity to elevated blood pressure and cardiac remodeling. Decades ago, The Framingham Heart Study established that both obesity and hypertension independently predict LVH and cardiovascular events. In addition, more recent longitudinal data have confirmed that higher BMI and waist circumference are associated with incident LVH, even after adjustment for blood pressure [41]. Our findings align closely with these results, with obese participants being significantly more likely to present with hypertension and LVH than their non-obese counterparts.

However, a notable observation in our cohort was the substantial burden of cardiovascular risk factors and early structural cardiac changes among the non-obese participants. Despite having BMI values below the obesity threshold, more than three-quarters of non-obese individuals met criteria for metabolic syndrome, over 85% had hypertension, and more than one-third exhibited LVH. Similar observations have been reported in population-based studies demonstrating that individuals with normal BMI may exhibit adverse metabolic profiles and increased cardiovascular risk, a phenomenon described as the metabolically unhealthy normal-weight phenotype [4]. Our data extend these observations by showing that non-obese individuals not only exhibit metabolic abnormalities but also a high burden of subclinical cardiac remodeling and further supports the concept of a metabolically unhealthy normal-weight phenotype.

6.4. Cardiometabolic phenotypes

An important novel finding of our study was the identification of four distinct cardiometabolic phenotypes using unsupervised cluster analysis, highlighting substantial heterogeneity in metabolic and inflammatory risk beyond BMI classification. In addition to classical high-risk phenotypes characterized by obesity with hyperglycaemia or dyslipidaemia, we identified a particularly important inflamed high-triglyceride phenotype characterized by elevated triglycerides, low HDL cholesterol, and increased hsCRP despite only moderate BMI. This phenotype demonstrates that significant cardiometabolic risk, including dyslipidaemia and systemic inflammation, can occur independently of severe obesity and may therefore remain undetected using BMI-based screening alone. Similar heterogeneity in metabolic risk has been demonstrated in previous cluster-based analyses, most notably by Ahlqvist et al., who identified distinct subgroups of adult-onset diabetes with markedly different metabolic characteristics and complication risks despite overlapping BMI

ranges, demonstrating that phenotype-based classification – integrating adiposity, metabolic, and inflammatory parameters – captures heterogeneity that is missed by BMI-based classification alone [42].

6.5. Structural Cardiac Changes and LVH

Another key finding in our study was the high prevalence of LVH, present in nearly half of participants and in more than one-third of non-obese adults. Waist circumference and systolic blood pressure emerged as the strongest independent predictors of LVH, consistent with recent population-based imaging studies showing that central adiposity and elevated blood pressure are primary determinants of left ventricular mass, independent of overall BMI [11]. Mediation analysis showed that hypertension partially mediates the association between waist circumference and LVH, indicating that central adiposity appears to contribute to myocardial remodeling partly through blood-pressure effects and partly through non-hemodynamic mechanisms. Together, these findings indicate that visceral adiposity promotes cardiac structural changes through combined hemodynamic load and adiposity-related metabolic stress, even among individuals who do not meet BMI-based criteria for obesity.

Taken together, these results show that systemic inflammation, adiposity, metabolic dysfunction, and early cardiac remodeling form interconnected components of cardiometabolic risk that extend beyond BMI-defined obesity. The interaction between visceral fat accumulation and inflammatory activity appears central to the development of glucose dysregulation, metabolic syndrome, and myocardial remodeling, therefore, the following section discusses potential pathophysiological mechanisms that may underlie these interrelated processes.

7. PATHOPHYSIOLOGICAL INTERPRETATION

The main pathophysiological pathways suggested by our data are summarized in Figure 12: excess visceral adiposity promotes insulin resistance, dyslipidaemia, arterial hypertension, and low-grade inflammation. It creates a vicious cycle: inflammation worsens lipid and glucose dysregulation, renal and vascular micro-damage further amplifies metabolic stress, and the resultant hemodynamic load leads to hypertension and structural cardiac changes (LVH). All of these mechanisms are consistent with the conceptual framework laid out by several obesity - CVD reviews, which emphasize adipose tissue inflammation, endothelial dysfunction and neurohormonal activation [43, 44]. Notably, the data we collected in our study extends these mechanisms into “non-obese” individuals and reinforces that specifically – central adiposity and inflammation – are the key driving forces rather than overall BMI per se.

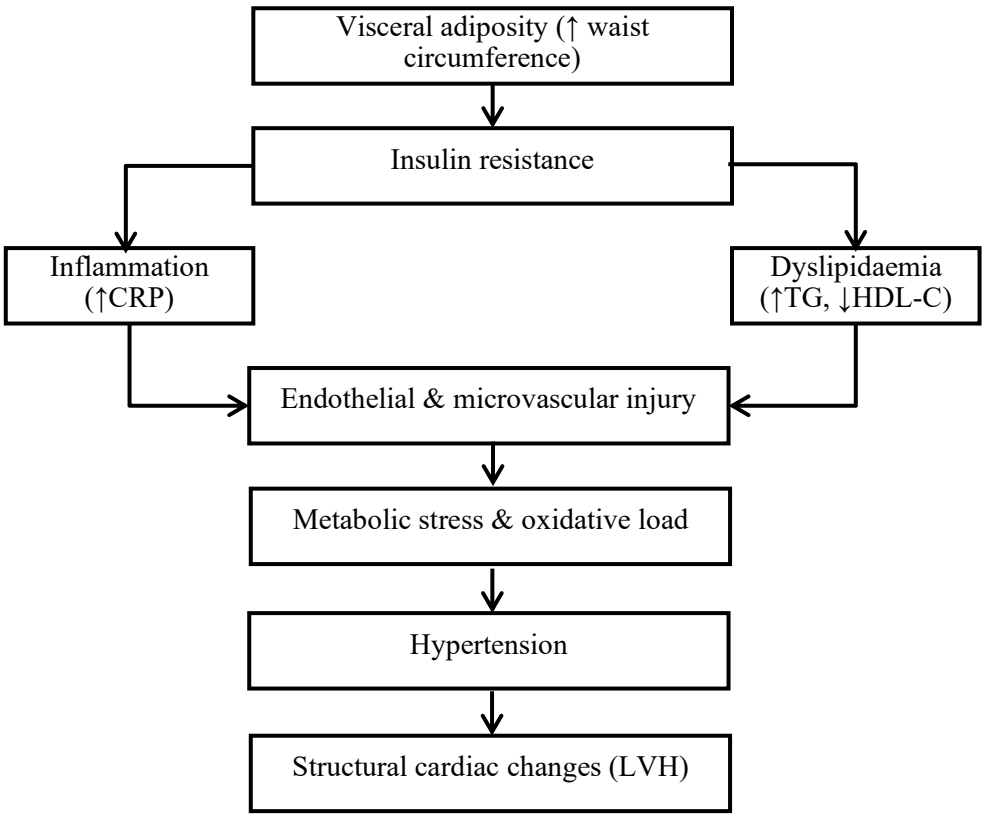


Figure 12. *Pathophysiological pathway linking central adiposity, inflammation, and cardiac remodeling. Schematic representation of the proposed mechanisms linking increased waist circumference (visceral adiposity) to left ventricular hypertrophy (LVH). Central adiposity contributes to insulin resistance, which promotes both systemic inflammation (↑CRP) and dyslipidaemia (↑triglycerides, ↓HDL-C). These processes lead to endothelial and microvascular injury, increased metabolic and oxidative stress, and the development of hypertension, ultimately contributing to structural cardiac changes.*

8. IMPLICATIONS FOR CLINICAL PRACTICE AND PREVENTION

Our findings have several important clinical implications. First, they reinforce the need to move beyond BMI as the primary metric for assessing cardiometabolic risk. While BMI remains a useful screening tool due to its simplicity and ease of measurement, it should be supplemented with measures of central adiposity (waist circumference), metabolic parameters (lipids, glucose, blood pressure), and potentially inflammatory biomarkers (hsCRP) to provide a more comprehensive risk assessment. Clinical guidelines are increasingly recognizing this need: the 2023 European Society of Hypertension guidelines [9] emphasize the importance of waist circumference measurement, and the 2021 American Heart Association scientific statement on obesity and cardiovascular disease [1] recommends routine assessment of body composition and metabolic health beyond BMI.

Second, the identification of distinct cardiometabolic phenotypes suggests opportunities for more personalized, precision medicine approaches to prevention and treatment. For example, individuals with the inflamed high-triglyceride phenotype may benefit from targeted interventions addressing

inflammation (e.g., lifestyle modification, consideration of anti-inflammatory agents) and dyslipidaemia (fibrates, omega-3 fatty acids), whereas those with the diabetic-obese phenotype may require intensive glucose-lowering therapy and weight loss interventions. Future research should investigate whether phenotype-guided treatment strategies improve outcomes compared to traditional risk factor-based approaches.

Third, our findings highlight the importance of early detection and intervention for subclinical cardiac remodeling. The high prevalence of LVH – even among non-obese individuals – suggests that echocardiographic screening may be warranted in high-risk populations, particularly those with central adiposity and arterial hypertension. Detection of LVH can prompt the use of more intense blood pressure management models and lifestyle intervention, potentially preventing progression to heart failure.

Fourth, the obesity-dependent nature of the inflammation-glucose association suggests that anti-inflammatory interventions may have differential efficacy across BMI strata. Recent trials of anti-inflammatory agents – such as colchicine and canakinumab – have demonstrated cardiovascular benefits [35,45], but these trials have not specifically examined whether effects differ by obesity status. Future studies should investigate whether obese individuals with elevated inflammatory markers represent a particularly responsive subgroup for anti-inflammatory therapies.

Several important questions remain unanswered and in need of further investigation. First, longitudinal studies are needed to determine whether the identified phenotypes predict differential cardiovascular outcomes and whether phenotype classification improves risk prediction beyond traditional risk scores. Second, intervention trials are needed to test whether phenotype-guided treatment strategies improve long-term patient outcomes. Third, mechanistic studies – including adipose tissue biopsy, assessment of adipokine profiles, and advanced imaging (cardiac MRI, visceral fat quantification) – are needed to further clarify the biological pathways underlying each phenotype. Fourth, studies in diverse populations are needed to determine whether these phenotypes generalize across ethnic groups and geographic regions, or whether population-specific phenotypes exist.

9. STRENGTHS AND LIMITATIONS

The main strengths of our study include the large sample size, real-world data derived from a structured cardiovascular prevention programme, standardized anthropometric and biochemical assessments, and inclusion of both obese and non-obese participants, allowing evaluation of cardiometabolic risk across BMI categories. The simultaneous assessment of metabolic, inflammatory, and echocardiographic parameters enabled integrated analysis of biochemical and structural cardiovascular risk.

Several limitations should be acknowledged. The cross-sectional design precludes causal inference.

Medication use, particularly lipid-lowering and antihypertensive therapy, was not included in the analysis and may have influenced lipid and blood pressure measurements. Renal marker analysis was not extensive, and longitudinal follow-up data on incident diabetes, regression of LVH, or cardiovascular events were not presented. Future prospective follow-up of this cohort will be valuable to determine how metabolic and inflammatory disturbances translate into long-term cardiovascular outcomes.

10. CONCLUSION

To conclude, our findings highlight that central adiposity, dyslipidaemia, hyperglycaemia, and systemic inflammation are closely interconnected components of cardiometabolic risk, extending beyond BMI-defined obesity:

1. hsCRP independently predicted fasting glucose with a markedly stronger effect among obese participants, indicating that the metabolic effects of systemic inflammation differ according to adiposity status.
2. The high prevalence of metabolic syndrome and cardiometabolic abnormalities even among the non-obese individuals indicates that inflammation and dyslipidaemia are associated with substantial metabolic risk independent of obesity, supporting the concept of a metabolically unhealthy normal-weight phenotype.
3. Measures of central adiposity and blood pressure were the strongest predictors of left ventricular hypertrophy in both obese and non-obese adults, highlighting that visceral adiposity is strongly associated with cardiac structural changes in the presence of elevated hemodynamic load.
4. The identification of distinct cardiometabolic phenotypes underscores the substantial heterogeneity of risk beyond BMI and reinforces the need for phenotype-based approaches to improve risk stratification.

Finally, this programme-based cohort from Lithuania provides valuable regional evidence and highlights the multifactorial nature of cardiometabolic risk in a high-risk prevention population.

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12. SUPPLEMENTARY MATERIALS

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DĖL MOKSLINIO TYRIMO

Vilniaus universiteto ligoninė Santaros klinikos sutinka, kad Vilniaus Universiteto Medicinos fakulteto VI kurso studentei **Gretai Žilinskaitei** rengianti mokslinį darbą „Kardiometabolinė rizika: uždegimo, metabolinio sindromo ir ankstyvų širdies struktūrinių pokyčių sąsajos“ būtų naudojamas nuasmenintų medicinos duomenų rinkinys. Už studentui teikiamų duomenų apimtį ir konfidencialumo užtikrinimą atsakinga darbo vadovė Jolita Badarienė.

Konfidencialios informacijos naudojimas turi būti užtikrintas.

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