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Translational Biomarkers for integrated Cardiovascular disease risk assessment: A multidisciplinary review with applications in precision medicine

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ABSTRACT

Aims: Cardiovascular disease (CVD) continues to be a leading cause of morbidity and mortality, significantly impacting healthcare systems and individual lives. This pragmatic review focuses on the assessment of CVD utilizing traditional and emerging risk factors that provide a basis for personalized medicine and precision nutrition, highlighting the knowledge and application of these insights for accurate risk diagnosis, individualized interventions, and precise outcome/evaluation prognosis.

Data synthesis: Critical biochemical markers such as lipid metabolism signatures, inflammatory molecules, endocrine mediators, homeostatic signals (including omics data), and lifestyle factors such as unhealthy dietary habits, physical inactivity, smoking, alcohol abuse, along with anthropometric variables and body composition measurements, play a pivotal role in assessing and managing CVD. This progression starts with early vascular and cardiac dysfunctions, advancing to atherosclerosis, and ultimately leading to cardiovascular events. Major adverse cardiovascular events, including myocardial infarction, stroke, and heart failure, highlight the need for effective and accurate risk stratification and objective assessment. Various CVD risk scores, such as the Framingham Risk Score, SCORE, and the Atherosclerotic Cardiovascular Disease Risk Calculator, provide valuable global frameworks for predicting individual risk based on recognized conventional factors. Additionally, omics markers—which encompass genomic, transcriptomic, epigenomic, proteomic, metabolomic, and metagenomic

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data—offer deeper insights into the molecular mechanisms underlying CVD, alongside novel lipidomic and immunomic determinants.
Conclusions: Integrating these various determinants and risk factors through a comprehensive approach is essential for advancing and implementing precision medicine and nutrition in the management of CVD.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of human morbidity and mortality worldwide, placing a significant burden on healthcare systems and individual lives [1]. Each year, more than 19 million people die from cardiovascular disease, with more than four in five deaths attributable to heart attacks and strokes and one-third of deaths occurring prematurely in people under 70 years of age [1,2]. Accordingly, CVD coherence and natural history includes acute and progressive cardiometabolic events associated with lifetime risks [3,4], stroke, acute coronary syndrome, myocardial infarction, heart failure, and arrhythmias [3]. On the other hand, progressive clinical events refer to the worsening of cardiovascular disease over time, leading to subclinical atherosclerosis, peripheral arterial disease, atrial fibrillation, chronic heart failure and recurrent myocardial infarction, among others [3,4].

The factors associated with the occurrence of CVD are diverse and involve pathophysiological, behavioral and environmental determinants [2], including manifestations such as high systolic blood pressure, elevated LDL-c levels, excessive adiposity, hyperglycemia, kidney dysfunction, as well as exposome factors such as environmental pollution, urban/climate exposures, smoking history, dietary imbalances, and sedentary behavior [5]. Indeed, there are metabolomics markers of cardiovascular risk which need to be analyzed deeply in the setting and clinical scenario [5]. In this context, residual risk is the risk that remains after the implementation of interventions aimed at the reduction and/or elimination of known and addressable variables that contribute to the disease [6]. On the other hand, the excess risk concept concerns the additional risk of disease due to specific factors, calculated as the difference between the current risk and the risk without those factors, assessing pathological outcomes that could be reduced by controlling or eliminating those factors [7].

Furthermore, LDL-c has been identified as a major etiological factor for CVD via many epidemiological and interventional studies, because LDL-c plays an important role in the pathogenesis of atherosclerosis as a stratification factor [8]. Patients with atherosclerosis are at an elevated risk for major adverse cardiovascular events [9], which include CVD mortality from cardiac events, arrhythmias, heart failure, endocarditis, aortic dissections and thromboembolic events [10]. Besides, LDL-c has mostly replaced total cholesterol as the primary lipid measure for predicting CVD risk [11]. Despite the clinical interest in lowering LDL-c to decrease cardiovascular risks, relevant residual risk remains due to other dyslipidemia disturbances, including elevated triglyceride-rich lipoprotein concentrations and low HDL-c circulating levels, underscoring the importance of assessing a broader lipid profile when stratifying cardiovascular risk [12].

A recent systematic review and meta-analysis suggests that in individuals with CVD, oxidized low-density lipoprotein (oxLDL) is significantly elevated in the presence of chronic inflammatory conditions [13]. This finding indicates that oxLDL may be a pivotal biomarker for risk stratification in these patients [13]. One of the pathophysiological mechanisms that has been described is the close relationship between platelets, oxLDL and native low-density lipoproteins, which leads to mild activation of the platelet cascade, together with the release of proatherogenic factors, initiating the formation of foam cells that progress to atheroma plaque [14].

Moreover, polymerase chain reaction for measuring diverse nucleic acids has been considered a highly valuable tool to early detect markers of CVD outcomes, as well as genome-exposome interactions that play a critical role in the onset and development of CVD [5]. Lifestyle habits such as unhealthy dietary habits, alcohol consumption, tobacco smoking, and physical inactivity, each of which is a CVD risk factor that, when combined, are not only additive but in some cases multiplicative [15]. Mechanisms linking the exposome to CVD include inflammatory responses due to chronic exposure to environmental factors triggering endothelial dysfunction and atherosclerosis. Also, excess oxidative stress, induced by pollutants and unhealthy lifestyles, can damage cardiovascular tissues [15].

A recent study has demonstrated the role of lysophosphatidylcholines (LPCs) in the immune regulation of monocytes showing that elevated levels of LPCs are associated with the modulation of immune checkpoint pathways, being involved in increased cardiovascular risks [16]. Thus, oxidized LPCs regulate mitochondrial bioenergetics in monocytes and macrophages that finally control tissue-specific glucose homeostasis with potential CVD implications [17]. In addition, epigenetic changes and associated metabolic dysfunctions, produced by unhealthy diet, physical inactivity, and chemical exposures disrupt metabolic processes, interacting with conditions such as obesity, diabetes, and hypertension, all significant clinical risk factors for atherosclerosis and CVD, among others [18–21].

Indeed, obesity is a cardiovascular risk factor that increases the risk of serious cardiac events. Weight loss through lifestyle changes and medication can reduce these risks, so it is essential to treat obesity, a complex disease, with integrated, multidisciplinary management involving endocrinologists, nephrologists and cardiologists to mitigate CVD events [22,23]. Notably, recent studies on the intricate relationship between the immune system and the induction of obesity revealed that innate lymphoid cells (group 2) – ILC2s – from intestinal origin, but not from white adipose tissue are involved in the induction of diet-induced obesity [24]. Here, macrophage-dependent mechanism(s) appear to be determinant for liver lipid-storage and insulin resistance impacting cardiovascular manifestations [25].

Moreover, the genetic makeup plays a pivotal role in regulating the cardiovascular system and impacting various cardiac risk factors [26]. Recent advances revealed several genetic variants associated with increased risk of CVD [26,27]. Specifically, single nucleotide polymorphisms within genes such as *SORT1*, *CDKN2A/2B*, *CELSR2-PSRC1-SORT1*, *FADS1*, and *LPA*, along with hereditary conditions like familial hypercholesterolemia, are recognized as key genomic factors contributing to CVD susceptibility, where a polygenic risk score based on different genes has been described as a key marker of CVD [28]. Moreover, gene-environment interactions are critical cornerstones in understanding the pathogenesis of CVD, where genomic medicine and pharmacogenomics could play integrative roles [27–29]. These interconnections underscore that genetic predispositions interact with environmental factors to influence the development and progression of cardiovascular related physio-pathological conditions, emphasizing the necessity of personalized precision approaches in managing and preventing CVD, which may be complemented by CVD risk omics signatures [29], such as transcriptomics, metabolomic and metagenomic tools and metabolomics are able to assess residual and excess CVD risk at an early stage with increasing medical precision for integrated intervention (Fig. 1).

Furthermore, the assessment of CVD risk entails both objective evaluations of residual risk, defined as the probability of an individual experiencing major adverse cardiovascular events due to coronary artery disease despite therapeutic intervention, and excess risk, which refers to the additional risk posed by specific factors or conditions. To be more precise, cardiovascular events that occur in patients despite optimal

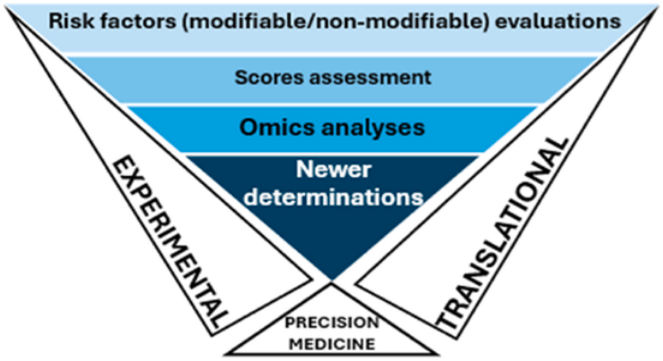

Fig. 1. Global cardiovascular disease assessment, experimental integration and translational progress.

risk factor control are called "residual risk" [6,30]. Some biomarkers such as C-reactive protein or the presence of subclinical atheromatosis have been identified as independent predictors of residual cardiovascular risk [6,30,31].

The residual risk of developing CVD can be quantified through a number of objective measures (Fig. 2), including lipid profile (triglycerides, lipoprotein(a), etc.), advanced inflammatory markers, glycemic control, blood pressure monitoring, genetic testing (polygenic risk scores), cardiac function biomarkers, imaging markers such as coronary artery calcium score, carotid intima-media thickness, ankle-brachial index, as well as lifestyle and behavioral assessments (physical activity monitors, dietary assessment tools, psychosocial stress and sleep quality scales) [32–34], together with quality of life indications as health surrogates. In contrast, the excess risk of CVD can be assessed using cardiovascular scores and risk calculators like the SCORE questionnaire or the Framingham risk score [7]. Additionally, genetic testing, behavioral assessments, and circulating homocysteine and lipid levels should be boosted for the assessment of residual and excess risk [7,35].

Subsequently, diverse biomolecules are extensively employed in various fields of medicine, including drug discovery and development, as well as safety assessment concerning CVD management [36]. These tools/measures serve as valuable indicators for disease progression, diagnostic accuracy, and therapeutic efficacy, while also monitoring adverse side effects in organisms, organs, and/or cells, as well as for disease prognosis [36,37]. It is noteworthy that biomarkers possess distinctive characteristics which define their specific applications, including diagnostic and monitoring biomarkers (Fig. 2), biochemical indicators, biomolecular markers of pharmacodynamic/response, outcome predictors, safety and susceptibility/risk biomarkers, which should be specific, sensitive, cost-effective, reliable, reproducible, and interpretable [36,37]. The progress made in biomarker research and the developments associated with CVD management have resulted in more accurate screening techniques and achieving more favorable clinical outcomes (Fig. 2), as evidenced by the advent of precision medicine [38].

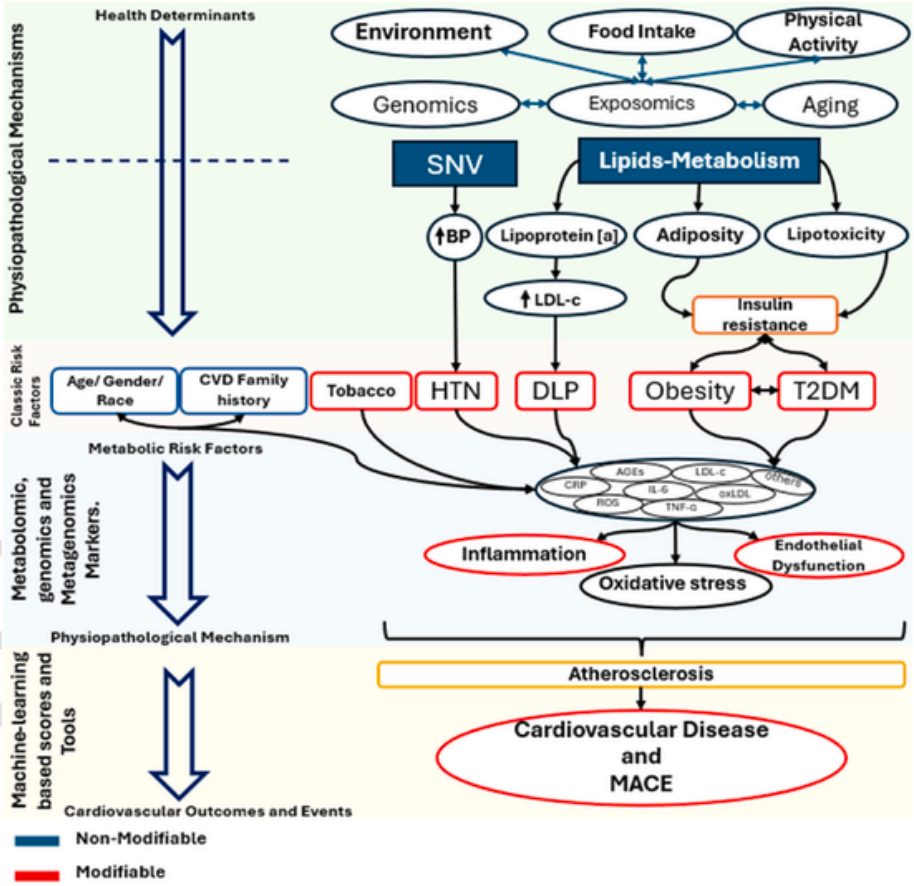

Fig. 2. Integrative graph of the natural history of cardiovascular disease and major adverse cardiovascular events. Advanced Glycation End Products (AGEs), Blood Pressure (BP), Cardiovascular Disease (CVD), C-Reactive Protein (CRP), Dyslipidemia (DLP), Hypertension (HTN), Interleukin-6 (IL-6), Low-Density Lipoprotein Cholesterol (LDL-C), Major Adverse Cardiovascular Events (MACE), Oxidized Low-Density Lipoprotein (oxLDL), Reactive Oxygen Species (ROS), Sympathetic Nervous System (SNV), Tumor Necrosis Factor-alpha (TNF-α), Type 2 Diabetes Mellitus (T2DM).

More specifically, traditional risk factors for CVD include male sex, older age, excess weight, hypertension, diabetes, elevated cholesterol levels, and a family history of CVD, as well as lifestyle factors such as sedentary behavior, unbalanced diet, smoking habits, and alcohol abuse [39]. Biological factors, including inflammatory, prothrombotic, endocrine, oxidative stress, and vascular/imaging markers, also contribute to the development of CVD [40], which need to be accounted for. These factors were initially identified by the Framingham Heart Study and subsequently incorporated into prediction equations to assist physicians in identifying individuals at an elevated risk and, consequently, optimizing cardiovascular prevention strategies, particularly in patients lacking established CVD [41]. Notable risk prediction models comprise SCORE, REYNOLDS RISK SCORE, ASCVD, and CUORE equation and algorithms [40].

Furthermore, "omics" signatures, such as genomic, transcriptomic, proteomic, epigenomic, metagenomic, and metabolomic data, provide insights into the genetic and molecular basis of CVD, thereby enhancing risk prediction and disease understanding [42]. A recent study has identified 23 metabolic biomarkers, mainly acylcarnitines, which are associated with cardiovascular events. Different patterns, such as heart failure-specific alterations in glycerophospholipids, improve risk prediction when combined with clinical markers [43]. In morbidly obese patients with a normal conventional lipid profile, advanced lipoprotein testing reveals atherogenic patterns associated with cardiac changes, inflammation, and insulin resistance. Parameters such as increased small LDL-P and LDL-P/HDL-P ratio are more predictive of the severity of left ventricular impairment than traditional risk factors [44].

In this context, precision medicine represents a novel and invaluable instrument for the management of CVD [45]. Precision medicine is defined as an evolving scientific approach to disease prevention and treatment that integrates an individual's genetic, environmental, and lifestyle factors [45,46]. Indeed, the precision management of CVD entails the utilization of both traditional and new markers to accurately predict, prevent, and treat the disease and for precision integrating prognosis and diagnosis [31].

This pragmatic review focuses on the assessment of CVD status, utilizing traditional and novel risk factors that provide a basis for personalized medicine and precision nutrition, highlighting the knowledge and application of these factors for preventive, management, and prognosis purposes. In conjunction, recent scientific advances such as cardiovascular risk scores and omics markers associated with diagnostic and prognostic monitoring may open the door to establish early precision personalized therapeutic intervention measures in selected patients, where the assessment of residual and excess CVD risk factors should be part of the translational implications.

2. Methodology

An extensive and comprehensive review was conducted through a rationalized search of scientific literature. The focus of this review was to collect classic CVD biomarkers such as lipoprotein(a), apolipoprotein A-1, triglycerides, cholesterol, C-reactive protein, insulin, among others and more specific traditional and emerging CVD risk factors. Risk estimators or scores (Framingham risk score, Regicor, ASCVD, Qrisk score, CUORE risk score, prospective cardiovascular Münster risk score, QD-Score5-year DAD risk equation, etc.) were collected for risk prediction. Omics signatures were recorded, information on genomics, proteomics, transcriptomics, metabolomics, epigenomics and metagenomics markers of CVD were also gathered. Due to the breadth of the topic, it was decided not to conduct a formal systematic review but an in-depth multi focused and structured narrative review for pragmatic purposes.

2.1. Search strategy

Independent exhaustive programmed analyses were performed based on credited electronic databases such as PubMed, Web of Science, Google Scholar, American Heart Association, European Society of Cardiology, and World Health Organization websites, including articles published during the last 2 decades (i.e. from 2002 and onwards), based on risk factors (biochemical and lifestyle-related), CVD scores and omics markers of CVD patients from a global perspective, following a flow chart design (Fig. 3).

The inclusion criteria for articles are related to individuals with CVD of any sex and age, with no restriction to European or Caucasian populations. The search attempted to follow the PRISMA recommendations [47] although the aim was not a systematic review; nevertheless, the rules decided before the start of the search are shown in Table 1. The points for PRISMA which were not accomplished were the following: No specify the criteria for grouping the studies for synthesis or the consultation date where no filters and limits were applied. The number of reviewers who screened each record and report, whether they worked independently, and details of any automation tools used in the process were not supervised. In addition, we have not listed the outcomes for which data were sought or other variables such as participant and inter-

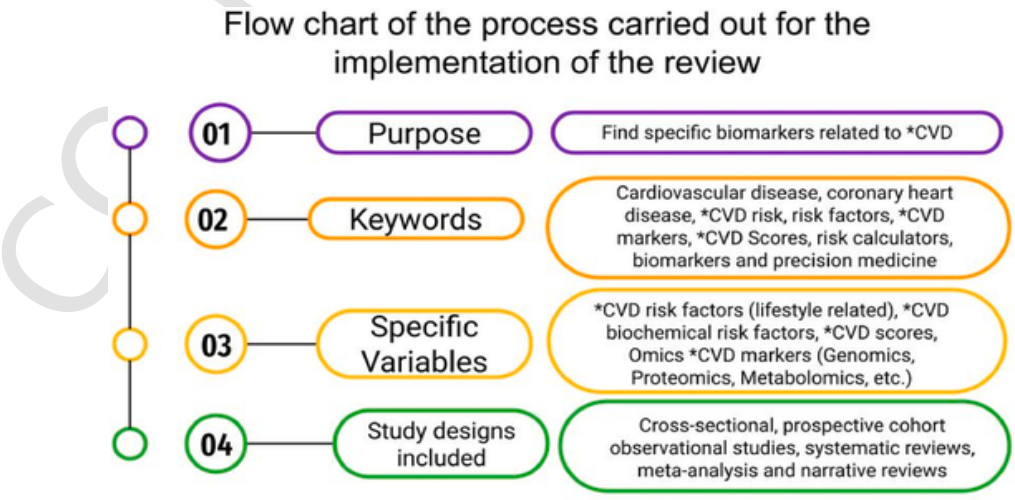

Fig. 3. Flow chart of the process carried out for the implementation of this pragmatic review.
*CVD, Cardiovascular disease.

Table 1
Features and criteria for including studies in the review, based on the PRISMA guidelines [47].

Title of review	Translational Biomarkers for integrated Cardiovascular Disease Risk assessment: A Pragmatic multidisciplinary Review with Applications in Precision Medicine
Population, or participants and conditions of interest	Cardiovascular disease patients with or without comorbidities No population restrictions were applied.
Interventions or exposures	No selected or removal specifically drivers.
Comparisons or control groups	Optional, not sought.
Outcomes of interest	Coronary artery disease, CVD, CVD risk factors, omics markers, CVD scores, precision medicine, biomarkers.
Setting	Healthy/Diseased individuals.
Study designs	Observational cross-sectional, prospective cohort studies, systematic reviews and meta-analysis on CVD risk factors.
Criteria for excluding studies in the review	Studies not correlated with CVD incidence and traditional or novel markers. Reports and articles which we could not retrieve the full text.
Search method	
Electronic databases/Information source	PubMed, Web of Science, Google Scholar, American Heart Association, European Society of Cardiology and the World Health Organization website.
Method of Review	
Details of methods	At least 2 searches in every database.
Quality assessment	Searches based on the PRISMA/Cochrane guidelines.
Narrative synthesis	1) CVD definition, prevalence, comorbidities, manifestations, complications. 2) Objectively measurement of CVD. 3) Traditional and novel CVD biomarkers. 4) Precision medicine.

vention characteristics and funding sources. The methods used to assess the risk of bias in the included studies were not specified. Finally, the effect measures (e.g., risk ratio, mean difference) for each outcome were not detailed, nor were any sensitivity analyses conducted to assess the robustness of the synthesized results due to the obvious difficulties for composers and that this pragmatic review is intended to provide information at a sequential glance.

The eligibility criteria for studies included in this search considered articles that included individuals diagnosed with CVD. Also, this comprehensive review included observational cross-sectional, prospective cohort studies, systematic reviews and meta-analyses evaluating major risk factors as well as traditional and novel biomarkers associated with CVD. The selected language was English or Spanish for all the research articles. The relevance of studies was assessed by using a hierarchical approach based on title, abstract, and full manuscript.

The main outcomes assessed in this review in relation to CVD and associated risk factors included lifestyle, biochemical markers, disease scores or estimators, and omics features (Table 2).

The traditional risk factors for CVD are classified into two categories: non-modifiable and modifiable factors. The non-modifiable factors include age and genetics backgrounds, while the modifiable factors encompass lifestyle and anthropometric factors, such as sedentary behavior, smoking, and dietary habits (Table 3).

Table 2
Main outcomes to be assessed from literature search

Key concept	Associated items
CVD risk factors (Lifestyle)	Sedentary lifestyle, Dietary intake, Smoking, Stress, Alcohol abuse, Anthropometric and nonmodifiable factors
CVD risk factors (Biochemical)	Lipid metabolism - related, Inflammatory - related, Prothrombotic- related, Endocrine-related, Vascular/Imaging-related, Miscellaneous
CVD scores or estimators	SCORE, Reynolds Risk Score, Framingham General CVD Risk Score, Regicor, ASCVD Edmonton Frailty scale, Assign risk score, QRISK3 score, etc.
CVD omics markers	Genomics, Proteomics, Metabolomics, Immunomics, Transcriptomics, Epigenomics and Metagenomics

3. Results

The major categories of CVD risk factors: lifestyle, biochemical, scores or estimating omics markers, are presented in Table 2. According to the CVD risk factors/lifestyle related, it has been shown that older age and males are reported to be at a greater risk of CVD (Table 3). In addition, family background played an important role as it was shown to be associated with recurrent CVD events [48]. Moreover, anthropometric parameters and more specifically, higher values of BMI, WC, WHtR, and fat mass index have been shown to be associated with higher CVD risk [49–52]. Likewise, long term sedentarism increases the CVD risk and higher dietary intake and/or blood concentrations of vita-

Table 3
Traditional CVD risk factors (general and lifestyle related). Measurement tools are some of the most used.

Markers	Measurement tools	Interpretation/Rational	Ref
Unmodifiable factors			
Age and sex	Questionnaire	Advanced Age – Male sex associated with higher CVD risk	[138]
Family Background	Medical Record	Associated with recurrent CV events	[48]
Modifiable factors			
Anthropometric			
BMI	BMI = Weight (kg)/Height (m)^2	Higher BMI associated with CVD risk	[49]
WC	FMT, AT	Higher WC associated with CVD risk	[50]
WHtR	FMT, SM or HMR	Higher WHtR associated with CVD	[51]
Fat mass index	DEXA, BIA, SC ADP, HW	FMI associated with CVD	[52])
Lifestyle			
Sedentary lifestyle	SRQ, AM, SBL DO, RST, HM	Long-term SL increases the CVD risk	[53]
Dietary intake	FFQs, 24HR, FR (or D), DAS, DO Biomarkers of Dietary Intake	Some foods and nutrients related to lower CVD risk	[54]
Smoking	SRQs, BoTE, CMO, UB SB, EMD, BV	Smoking is associated with CVD	[55]
Stress	SRQs, SAS, PM, BA, PA, Biofeedback and Neurofeedback	Stress associated with atherogenesis	[56]
Alcohol abuse	AUDIT, CAGE Questionnaire TLFB, DDQ, ACD	Alcohol abuse associated with CVD risk	[57]

ACD, Alcohol Consumption Diaries; ADP, Air Displacement Plethysmography; AM, Activity Monitors; AR, Administrative records; AT, Anthropometric Tape; AUDIT, Alcohol Use Disorders Identification Test; BA, Behavioral Assessments; BIA, Bioelectrical impedance analysis; BMI, Body Mass Index; BoTE, Biomarkers of Tobacco Exposure; BV, Biochemical verification; CAGE, CMO, Carbon Monoxide (CO) Monitoring; CT, Clinical Trials; DAS, Dietary Assessment Software; DDQ, Daily Drinking Questionnaire; DEXA, Dual-energy X-ray Absorptiometry; DO, Direct Observation; DS, Demographic Surveys, HER, Electronic Health Records; EMD, Electronic Monitoring Devices; ES, Epidemiological surveys; FFQs, Food Frequency Questionnaires; 24R, 24-Hour Dietary Recall; FMI, Fat mass index; FMT, Flexible Measuring Tape; FR (or D), Food Records (or Diaries); HM, Heart monitoring; HMR, Height Measuring Rod; HW, Hydrostatic Weighing; OFHT, Online Family History Tools; PA, Psychological Assessments; PM, Physiological Measures; RST, Remote Sensing Technologies; SAS, Stress Assessment Scales; SBL, Sedentary Behavior Logs; SB, Salivary Biomarkers; SC, Skinfold Calipers; SL, Sedentary Lifestyle; SM, Stadiometer; SQ, Structured Questionnaires; SRQs, Self-Reported Questionnaires; TLFB, Timeline Follow-Back; UB, Urinary Biomarkers; WC, Waist Circumference; WHtR, Waist-to-height ratio.

min C, carotenoids, and α-tocopherol (as markers of fruit and vegetable intake) were associated with reduced risk of CVD [53,54]. Smoking also increases CVD risk [55] and psychological stress is associated with atherogenesis [56]. Another factor is alcohol abuse which increases the risk of developing CVD [57] (Table 3).

Regarding lipid metabolism factors, high concentrations of Lp(a) have been associated with a greater risk of ischemic CVD, aortic valve stenosis and Myocardial infarction [58] and apolipoprotein A-1 has been related with an increased risk of CVD events [59]. Higher APOB levels were associated with the risk of heart and vascular vessel disease (Table 4A). LDL particle also indicates high CVD risk [53] and elevated triglycerides were associated with high overall risk for atherosclerotic cardiovascular disease [60]. In addition, other lipid metabolism factors such as cholesterol, cholesteryl ester transfer protein, Lp-PLA2, etc. May increase the risk for heart attack or stroke and predict future CVD (Table 4A).

In terms of inflammatory related factors, high-sensitivity C-reactive protein is a marker of inflammation that predicts incident of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death (Table 4B). In addition, the levels of IL-6, IL-18 were associated with high CVD risk, but IL-10 was protective against CVD [61]. Furthermore, increased TNF–α with IL-6 were correlated with CVD risk [62], ICAM–1 was associated with endothelial damage [63] and myeloperoxidase was found to be correlated with coronary artery disease [64] (Table 4B). In addition, VCAM-1 can predict the CVD mortality and high ferritin levels were related to high CVD risk [65,66] On the other hand, regarding to endocrine related factors, high Insulin leads to atherosclerosis, and low adiponectin levels also were associated with CVD [67,68]. Moreover, it is observed that leptin resistance is associated to CVD risk as well as fasting plasma glucose and other endocrine factors such as E-selectin, NT-proBNP, Chimerin etc. [69–74] (Table 4B).

Concerning prothrombotic related factors, increased plasma fibrinogen concentration may be the cause of the development of atherosclerotic lesions (increased risk of atherothrombosis) [75] (Table 4C). D-dimer is a prognostic biomarker for major adverse cardiovascular events and Von Willebrand factor is predictive for adverse cardiac events [76,77]. In addition, vascular/imaging related markers were included and were shown to be predictive factors for CVD events. Carotid intima media thickness [78], coronary artery calcium [79] and Ankle-brachial index have been used as a vascular/imaging markers of atherosclerosis for cardiovascular risk assessment [80]. Relating to miscellaneous markers, sialic acid is correlated with CVD risk while high desacyl ghrelin is associated with lower CVD risk (Table 4C).

Several risk scores have been developed and are being used for cardiovascular risk prediction. Some of the most common CVD scores or risk estimators (SCORE, SCORE2 and SCORE2-OP, REYNOLDS RISK SCORE, FRAMINGHAM CVD RISK SCORE, REGICOR, ASCVD, Pooled cohort equations calculator, Edmonton Frailty scale, Assign risk score, QRISK3 score, CUORE risk score, PROCAM Risk Score, 5-year DAD risk equation) are attached on (Table 5) in order to specify the prognostic tools needed to identifying individuals at higher risk and prevent cardiometabolic abnormalities. SCORE (Systematic Coronary Risk Evaluation) predicts the 10-year risk of cardiovascular and takes into account age, sex, Systolic Blood Pressure, total cholesterol, and smoking [81]. Similarly, Reynold's Risk Score estimates 10-year risk of cardiovascular events and takes into account age, sex, systolic blood pressure, total cholesterol, HDL-c, etc. And it was found to have high predictive value [82]. In addition, Framingham risk score and other cardiovascular risk prediction equations are mentioned in this rational review (Table 5).

Finally, newer CVD biomarkers and especially omics markers were found to affect CVD risk morbidity and mortality (Table 6). Regarding the field of genomics, *SORT1*, *SORT1* regulates LDL-c levels and is correlated with CAD risk and *CDKN2A/2B* is associated with CAD and peripheral vascular disease [83,84]. *CELSR2-PSRC1-SORT1* was found to be related with CVD risk, *FADS1* was correlated with high CVD risk, and

Table 4A
Traditional Biochemical CVD Risk factors in relation to lipid metabolism markers.

Markers	Measurement tool	Interpretation/Rationale	Ref
Lipid metabolism related			
Lipoprotein(a)	ELISA, HPLC, Nephelometry Immunoassay Kits	Higher lipoprotein(a) associated with myocardial infarction	[58]
Apolipoprotein A-1	ELISA, HPLC - MS, WB	Higher ApoA1 - predictor for ischemic heart disease	[11]
APOB	ELISA, WB, HPLC Immunoassay Kits	Higher Apo B associated with risk of heart and blood vessel disease	[11]
LDL particle	NMR Spectroscopy, IMA, GGE, UC, LPT	LDL particle indicates high CVD risk	[151]
Triglycerides	ECA, Chemical Titration HPLC - MS, GC - MS	Elevated TG levels associated with CVD risk	[60]
Chol	LP, POCTD, HCTK, SCTK	Higher TC improve CVD risk prediction	[152]
CETP	ELISA, RIA, WB, CETP Activity Assay, MS	Lower CETP levels associated with decreased CVD risk	[153]
Lp-PLA2	ELISA, Activity Assays HPLC - MS, WB, POCT	Increased concentrations of Lp-PLA2 predict future CVD	[154]
Small-dense LDL	GGE, NMR Spectroscopy, IMA, PAGE, LPT	sdLDL-C proportion is a marker for CVD	[155]
Paraoxonase-1	EAA, AAA, ELISA, WB, HPLC - MS	Low PON1 activity associated with CVD risk	[156]
Plasma PLTP	EAA, PTA, ELISA, WB, MS	Plasma PLTP activity is associated positively with CVD risk	[157]
Lysophosphatidylcholines (LPCs)	MS, ELISA	Levels of LPCs are associated positively with CVD risk	[158]
PCSK9	ELISA, WB, MS, FC, IHC, RIA, SPR	PCSK9 associated with acute CVD events	[159]

AAA, Arylesterase Activity Assays; CETP, Cholesteryl ester transfer protein; EAA, Enzyme Activity Assays; ECA, Enzymatic Colorimetric Assay; ELISA, Enzyme - linked immunosorbent assay; FC, Flow Cytometry; GC–MS, Gas Chromatography Mass Spectrometry; GGE, Gradient Gel Electrophoresis; HDL-C, high-density lipoprotein cholesterol; HPLC–MS, High Performance Liquid Chromatography-Mass Spectrometry; HCTK, Home Cholesterol Test Kits; IHC, Immunohistochemistry; IMA, Ion Mobility Analysis; LDL-C, Low-density lipoprotein cholesterol; LP, Lipid Panel; LP-PLA2, Lipoprotein-associated Phospholipase A2; LPT, Lipoprotein Profiling Tests; MS, Mass Spectroscopy; NMR, Nuclear Magnetic Resonance; PAGE, Polyacrylamide Gel Electrophoresis; PCSK9, Proprotein convertase subtilisin/kexin type 9; POCT, Point-of-Care Testing; POCTD, Point-of-Care Cholesterol Testing Devices; PLTP, phospholipid transfer protein; PTA, Phospholipid Transfer Assays; RIA, Radioimmunoassay; SCTK, Smartphone-Compatible Testing Kits; SPR, Surface Plasmon Resonance; TC, Total Cholesterol; TG, Triglycerides; UC, Ultracentrifugation; WB, Western Blotting.

LPA was also linked with CVD risk [85–87]. Regarding to proteomics, TNNT2 is a strong biomarker of myocardial infarction [88] and other markers such as BNP, C-reactive protein, myeloperoxidase, and metalloproteinase, were associated with cardiac events and classical CVD factors [89–91] as described (Table 6).

As regards the field of metabolomics, trimethylamine N-oxide (TMAO), a gut derived metabolite, has been associated with atherosclerotic burden and peripheral artery disease [92]. These effects could be significantly influenced by the content of specific lysophosphatidyl-

Table 4B
Traditional Biochemical CVD Risk factors in relation to inflammation and endocrine markers.

Markers	Measurement tool	Interpretation/Rational	Ref
Inflammatory - related			
hsCRP	ELISA, Immunoturbidimetry and Immunonephelometric HSI, POCT, HPLC	Higher hsCRP associated with CVD risk	[160]
Interleukins 6, 10, 18	ELISA, MI, FC, qPCR IHC	Oversecretion of IL-6, IL-18 associated - CVD risk/Low IL-10 associated with CVD	[61]
TNF-α	ELISA, MI, FC, qPCR, IHC	Increased TNF - α correlated with CVD risk	[62]
ICAM-1	ELISA, FC, IHC, WB, SPR	ICAM-1 associated with endothelial damage	[63]
Myeloperoxidase	ELISA, Immunofluorescence FC, WB, AA	Elevated levels of MPO related with CAD	[64]
VCAM-1	ELISA, FC, IHC, WB, SPR	VCAM-1 predicts CVD mortality	[65]
Ferritin	ELISA, CLIA RIA, Immunoturbidimetry POCT	Increased SF levels increased CVD risk	[66]
Hepcidin	MS, ELISA	Increased risk and mortality	[161]
Endocrine-related			
Insulin	RIA, ELISA, CLIA, ECLIA, LC-MS	High insulin levels lead to atherosclerosis	[67]
Adiponectin	ELISA, RIA, LA, WB	Low adiponectin levels associated with CVD	[68]
Leptin	ELISA, RIA, LA, WB	Conflicting findings on hyperleptinemia or leptin resistance contribution to CVD	[69]
Fasting plasma glucose	BCM, Laboratory-Based Tests OGTT, CGM, HbA1c Testing	Fasting glucose leads to CVD risk	[70]
E-selectin	ELISA, FC, WB, IHC, qPCR	Higher E-Selectin levels connected to atherosclerosis	[71,72]
NT-proBNP	Immunoassays, POCT Devices, AIA, MS	High NT–proBNP concentration associated with CHD	[73]
Chemerin	ELISA, WB, IHC, qPCR	Chemerin - predictive marker of atherosclerosis	[74]
Cystatin-C	ELISA, CLIA, Nephelometry Turbidimetry	High cystatin-C related to heart disease	[162]
HOMA-IR	BCM, IM	High levels of HOMA-IR is an independent CVD risk factor	[163]
TyG Index	RIA and EAI.	High levels of TyG Index are an Independent CVD Risk Factor	[164]
Atherogenic Index of Plasma (AIP)	LP, POCT, LCS	AIP – predictive biomarker of CVD	[165]
Castelli's Risk Index (CRI)	LP, POCT, CIT	CRI associated with atherosclerosis and CVD	[166]
TG/HDL-C ratio	LP, POCT, OCDH	High TG/HDL-C associated with CVD	[167]
apoB/apoA1	LP, POCT, OCDH	High apoB/apoA1 associated with CVD	[168]
Fatty Liver Index	ECA, Chemical Titration HPLC - MS, GC - MS	High Fatty Liver Index associated with CVD	[169]
Hepatic steatosis index	ELISA	High Hepatic steatosis index associated with CVD	[170]

AA, Activity Assays; AIA, Automated Immunofluorescence Assays; BCM, Blood Glucose Measurement; CAD, Coronary Artery Disease; CE, Capillary Electrophoresis; CGM, Continuous Glucose Monitoring; CHD, Coronary heart disease; CLIA, Chemiluminescent Immunoassay; CIT, Complementary Imaging Tools; EAI, Enzymatic Assays Immunoassays; ECA, Electrochemiluminescence Assisted or Advanced Chromatography Assay; ECLIA, Electrochemiluminescence Immunoassay; FC, Flow Cytometry; HOMA-IR, homeostatic model assessment for Insulin Resistance; HPLC - High-Performance Liquid Chromatography; hsCRP, High-Sensitivity C-Reactive Protein; HSI, High-Sensitivity Immunoassays; ICAM–1, Intercellular Adhesion Molecule 1; IHC, Immunohistochemistry; IM, Insulin Measurement; LAA, Latex Agglutination Assays; LA - Luminex Assay; LC–MS, Liquid Chromatography - Mass Spectrometry; LCS, Laboratory Calculators and Software; LP, Lipid Panel; MI, Multiplex Immunoassay; MPO, Myeloperoxidase; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; OCDH, Online Calculators and Digital Health Apps; OGTT, Oral Glucose Tolerance Test; POCT, Point-of-Care Testing; qPCR, Quantitative Polymerase Chain Reaction; RCAA, Ristocetin Cofactor Activity Assay; RIA, Radioimmunoassay; SPR, Surface Plasmon Resonance; TNF-α, Tumor Necrosis Factor-alpha; TyG, Triglyceride-Glucose Index; VCAM–1, vascular cell adhesion molecule 1; WB, Western Blotting; SPR, Surface Plasmon Resonance.

cholines (i.e., 16:0 or 18:2), which result prone to oxidation affecting monocyte/macrophage's proinflammatory and metabolic activity. Despite LPC's serum levels appear not to change in coronary artery disease, LPC inhibition can significantly contribute to surmount and/or avoid the disease through endothelial progenitor cells revitalization [93]. In this context, recently identified metabolites such as itaconate (s) received significant interest due to its therapeutic value and potential as biomarker in CVDs [94].

Branched-chain amino acids and more specifically, elevated concentrations of circulating Isoleucine were associated with increased risks of CVD, whereas Valine and Leucine did not appear to be associated with CVD incidence [95] (Table 6). Additionally, CVD is attributable to other metabolomic markers such as oxLDL, advanced glycation end products (AGEs) and fatty acid metabolites [96,97]. Transcriptomics such as miR-21, miR-155 are linked with cardiac events or death [98,99] while downregulated expression of miR-126 has been associated with highly prevalent cardiovascular risk factors such as arterial hypertension and diabetes mellitus [100].

Epigenomics are factors aligned with high CVD risk. In detail, DNA methylation is associated with CVD development [101], histone modifications promote CVD [102], while microRNA expressions are involved in the development of atherosclerosis and thrombosis [103] and non-coding RNA modifications are important contributors to CVD [104] incidence (Table 6).

Further, metagenomics, for instance, inflammatory microbiota, *Ruminococcus*, *Akkermansia* and other bacteria were highlighted to have a direct association with the CVD and cardiovascular artery disease progression [105–107] under different conditions (Table 6).

All these parameters are interconnected as CVD risk is influenced by a combination of lifestyle-related factors, biochemical markers, and omics data, which are integrated into risk scores to estimate an individual's overall risk. They help healthcare providers to develop comprehensive and personalized approaches to CVD prevention and management, whose integrated interpretation in fundamental for precision nutrition and medicine.

3.1. Some mechanistic insights

While diabetes and insulin resistance are multifactorial [108,109], it is now clear that glucose overload, especially when chronic, plays major roles in the etiology and development of these metabolic disorders [110]. Among the key consequences of chronic glucose overload is an apparent stiffness in mitochondrial substrate selection [110]. This phenomenon is termed "metabolic inflexibility" and ultimately leads to "metabolic gridlocks," in which, for example, mitochondria are overloaded, and carbon flux is perturbed [110]. It must be underscored that

Table 4C
Traditional Biochemical CVD Risk factors in relation to prothrombotic, vascular/imaging and miscellaneous markers.

Markers	Measurement tool	Interpretation/Rational	Ref
Prothrombotic- related			
Fibrinogen	CM, Immunoassays, RI	fibrinogen associated with Atherosclerosis	[75]
D-dimer	ELISA, LAA, Immunoturbidimetry AIA, POCT	High D-dimer levels associated ischemic heart disease and thromboembolism	[76]
Von Willebrand factor	ELISA, RCAA, Multimer Analysis VWF, Activity Assays	VWF is predictive for adverse cardiac events	[77]
Homocysteine	HPLC, EAI, GC-MS	High HC associated with atherosclerosis and CVD	[171]
Haptoglobin	Immunoturbidimetry Immunonephelometry ELISA, WB, CE	Hp is a risk factor for CV events	[172]
Asymmetric Dimethylarginine (ADMA)	HPLC, LC-MS, ELISA, RIA, CE, POCT	Higher levels of ADMA associated with CVD risk	[173]
Fatty Acid Binding Protein 4 (FABP4)	ELISA, RIA, WB, MS, IHC, MAP, POCT	FABP4 associated with CVD risk and mortality	[174]
Vascular/imaging -related			
CIMT	UI, MMT, EDA	CIMT of 1 mm or more associated with CHD risk	[78]
CAC score	CT, SAT, ACSS, MC	High CAC levels associated with CVD	[79]
Ankle-brachial index	DU, BPC, Automated ABI Systems, Handheld ABI Devices	Low ABI is associated with CV disease	[80]
Miscellaneous			
Sialic acid	CA, HPLC, EAI, CE	Elevated sialic acid correlated with CVD	[175]
Desacyl ghrelin	ELISA, RIA, LC-MS, WB	Des-acyl ghrelin lowers the CVD risk	[176]

ACSS, Automated Calcium Scoring Systems; AIA, Automated Immunofluorescence Assays; BCM, Blood Glucose Measurement; BPC, Blood Pressure Cuffs; CA, Colorimetric Assays; CAC score, Coronary artery calcium score; CE, Capillary Electrophoresis; CGM, Continuous Glucose Monitoring; CIMT, Carotid intima-media thickness; CM, Clauss Method; CT, Cardiac Computed Tomography; DU, Doppler Ultrasound; EAI, Enzymatic Assays Immunoassays; ECLIA, Electrochemiluminescence Immunoassay; EDA, Edge Detection Algorithms; ELISA, Enzyme-linked immunosorbent assay; FC, Flow cytometry; GC MS, Gas Chromatography-Mass Spectrometry; HC, Homocysteine; HPLC, High-Performance Liquid Chromatography; HIS, High-Sensitivity Immunoassays; IHC, Immunohistochemistry; IM, Insulin Measurement; LAA, Latex Agglutination Assays; LA, Luminex Assay; LC MS, Liquid Chromatography-Mass Spectrometry; MAP, Multiplex Assay Platforms; MS, Mass Spectrometry; MC, Manual Calculation; MI, Multiplex Immunoassay; MMT, Manual Measurement Tools; OGTT, Oral Glucose Tolerance Test; POCT, Point-of-Care Testing; qPCR, Quantitative Polymerase Chain Reaction; RCAA, Ristocetin Cofactor Activity Assay; RIA, Radioimmunoassay; RI, Radial Immunodiffusion; SAT, Software Analysis Tools; SAT, Software Analysis Tools; SPR, Surface Plasmon Resonance; UI, Ultrasound Imaging; VWF, von Willebrand Factor; WB, Western Blotting.

mitochondrial dysfunction is exacerbated by age [111] and that a proper, plant-based diet slows down this phenomenon [111].

In any case, mitochondrial dysfunction has immediate untoward consequences. The first and most notable one is the onset of oxidative stress [112], in which the flux of oxidants from mitochondria overloads their [mostly enzymatic] scavenging system [112]. Furthermore, mitochondrial dysfunction can impair the function of the tricarboxylic acid (TCA) cycle, a central metabolic pathway in cellular energy production [113]. This impairment can lead to a cascade of detrimental effects, including reduced ATP synthesis, increased oxidative stress [112], and altered cellular signaling. The TCA cycle relies on mitochondrial function to generate essential molecules like NADH and FADH2, which are crucial for oxidative phosphorylation to produce ATP [113].

Table 5
Main characteristics of the most widely used CVD Scores or risk estimators.

Index	Data	Interpretation/Rational	Ref
SCORE	Age, sex, SBP, TC and smoking	Very High risk: >10 %, High risk: 5–9 %, Moderate risk: 1–4 %, Low risk: <1 %	[81]
SCORE 2 (40–49 years)	Age, gender, tobacco consumption, diabetes, SP, non-HDL-C, TC and European geographic region	High: ≥7.5 % Moderate: 2.5–7.5 % Low: <2.5 %	[177]
SCORE 2 (50–69 years)	Age, gender, tobacco consumption, diabetes, SBP, TC, non-HDL-C, and European geographic region	High: ≥10 %, Moderate: 5–10 %, Low: <5 %	[177]
SCORE2-OP	Age, gender, SBP, TC, smoking status, diabetes, family history of CVD, use of antihypertensive medication, renal function and European geographic region	High: ≥15 %, Moderate: 7.5–15 %, Low: <7.5 %	[177]
REYNOLDS RISK SCORE (RRS)	Age, gender, TC, HDL-c, SBP Smoking status, hsCRP level, family history of premature heart disease (before the age of 60)	High: RRS ≥10 %, Medium: 5 %≤ RRS <10 %, Low: RRS <5 %	[82]
FRAMINGHAM GENERAL CVD RISK SCORE **10-year risk**	Age, gender, TC, HDL, smoking habits, and SBP, Diabetes	High risk: >20 %, Intermediate risk: 10–20 %, Low risk: <10 %	[178]
FRAMINGHAM GENERAL CVD RISK SCORE **30-year risk**	Age, gender, TC, HDL, smoking habits, and SBP, Diabetes	High risk: ≥40 %, Moderate risk: 13–39 %, Low risk: ≤12 %,	[179]
REGICOR	Age, sex, SBP, DBP, TC, HDL-C, and smoking status.	High risk: <10 %, Moderate risk: 5–9.9 %, Low risk: <5 %	[180]
ASCVD	Age, sex, race, TC, HDL, DM, SBP, BP treatment and current smoking status. Race (Black or non-Black	High risk >20 %, Intermediate risk 7.5–20 %, Borderline risk: 5–7.4 % Low risk: 0–4.9 %	[181]
Pooled cohort equations calculator	Age, sex, SBP, treatment for hypertension, TC, HDL-C, history of T2DM and smoking status	High (≥20 %), Intermediate (7.5 % to <20 %), Borderline (5 % to <7.5 %), Low risk (<5 %)	[182]
Edmonton Frailty scale	Cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, functional performance	Severely frail (≥10), Moderately Frail (8–9), Mildly frail (6–7), Vulnerable (4–5), Fit (0–3)	[183]
Assign risk score	Age, sex, SBP, TC, T2DM, smoking, social deprivation and family history of CVD	High risk: >20 %, Moderate risk: 10–20 %, Low risk: <10 %	[184]
QRISK3 score	Ethnicity, family history, Cholesterol/HDL ratio, BMI, hypertensive medication, rheumatoid arthritis, chronic kidney disease and atrial fibrillation	High Risk: >20 %, Moderate Risk: 10–20 %, Low Risk: <10 %	[185]
CUORE risk score	Age, sex, SBP, TC, HDL-C, presence of DM2, treatment for hypertension and smoking status	High risk: ≥20 %, Medium risk: ≥5 % and <20 %, Low risk: <5 %	[186]

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Table 5 (*continued*)

Index	Data	Interpretation/Rational	Ref
PROCAM Risk Score	Age, SBP, LDL-C, HDL-C, TGs, presence of DM2, family history of MI and smoking status	High risk (>20 %), Medium risk (10–20 %), Low risk (<10 %)	[187]
Five-year DAD risk equation	Age, gender, TC and HDL, smoking status (current or past), BP, history of diabetes, family history of CVD, and exposure to indinavir, lopinavir and abacavir	Very high score (>10 %), High score (5–10 %), Moderate score (1–5 %), Low score (<1 %)	[187]

BMI, Body mass index; BP, Blood pressure; CVD, Cardiovascular disease; DBP, Diastolic blood pressure; DM, Diabetes mellitus; HDL, High Density Lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, Low Density Lipoprotein; MI, Myocardial infarction; SBP, Systolic blood pressure; T2DM, Type 2 Diabetes Mellitus; TC, Total cholesterol; TG, Triglycerides.

Finally, the accumulation of harmful intermediates like methylglyoxal [114] and AGEs [114] is a significant contributor to cardiometabolic disorders (and the aging process) [115]. These molecules, formed through non-enzymatic reactions [114], can cause cellular dysfunction [114,115] and, as noted, contribute to the development of conditions like diabetes, cardiovascular disease, and neurodegenerative disorders [114,115].

In summary, an inordinate consumption of high-glycemic index foods causes cardiometabolic disorders [116] via a plethora of mechanisms including endothelial dysfunction and metabolic inflexibility. A plant-based diet and low-glycemic load meals should be promoted to lower the cardiometabolic burden [117].

Emerging evidence emphasizes the critical role of epigenetics in cardiovascular and other chronic diseases, including regulatory methylation phenomena and histone post-translational covalent modifications [118]. Thus, acetylation of nuclear proteins, including histones, metabolic enzymes, and SIRT-regulated targets, has been implicated in physiopathological processes such as cardiomyocyte energy imbalance, impaired inflammatory responses, and endothelial dysfunctions [119,120]. Acetylation-driven alterations modulate key cellular functions like mitochondrial respiration, fatty acid oxidation, and the expression of proinflammatory genes [121,122] (3–4).

Furthermore, some epigenetic processes are increasingly recognized as contributors to residual cardiometabolic risk, which persists despite control of recognized risk factors such as LDL cholesterol, blood pressure, and glycemia [123]. For instance, dysregulation of sirtuin activity, particularly SIRT3 in mitochondria and SIRT1 in the nucleus, can impair cellular resilience by altering acetylation states of proteins involved in oxidative metabolism and vascular tone [119,122].

Additionally, epigenetic patterns have been associated with a proatherogenic and inflammatory phenotype in vascular tissues, suggesting that such epigenetic and post-translational mechanisms may underlie residual cardiovascular risk [122].

Altogether, these findings support the notion that targeting genetic and epigenetic-related regulatory networks could offer novel therapeutic opportunities for moderating residual risk in cardiometabolic-associated diseases [123,124].

4. Discussion

Personalized and precision medicine and nutrition are innovative concepts that can benefit from approaches that integrate multiple factors and determinants and tailor clinical recommendations to an individual's unique genetic makeup, lifestyle, and health status [125,126]. Personalized medicine and nutrition focus on individuality dietary plans based on personal characteristics such as age, gender, medical history, and preferences [127] while precision nutrition takes this notion a step further to holistically convey genetic, microbiome, meta-

Table 6
Omics signatures and determinants for prediction and management of CVD.

Index	Research tools	Interpretation/Rational	Ref
Genomics			
rs10757274 (SORT1)	PCR and Genotyping Arrays	Regulates LDL cholesterol levels and CAD risk	[83]
rs1333049 (CDKN2A/2B)	PCR and Genotyping Arrays	Linked with CAD risk	[84]
rs646776 (CELSR2-PSRC1-SORT1)	PCR and Genotyping Arrays	Associated with increased CVD risk	[85]
rs1746048 (FADS1)	PCR and Genotyping Arrays	Correlated with CHD risk	[86]
rs6725887 (LPA)	PCR and Genotyping Arrays	Negative association between the rs6725887 risk allele (C) and carotid IMT	[87]
Proteomics			
Troponin T (TNNT2)	hsTnT assay	TNNT2 is a biomarker of MI	[88]
BNP	BNP Immunoassay	BNP associated with increased stroke risk	[89]
CRP	hsCRP Assay	CRP is a predictor of CVD	[90]
MPO	ELISA, CLIA, Immunoturbidimetry or Immunonephelometry	MPO associated with cardiac events	[91]
MMPs	ELISA, Multiplex Immunoassays (e.g., Luminex)	MMPs are associated with the classical CVD factors	[188]
Metabolomics			
TMAO	HPLC/LC-MS	TMAO is associated to PAD severity	[92]
BCAAs	HPLC	Higher Isoleucine associated with CVD but Valine and Leucine not	[95]
oxLDL	ELISA	OxLDL increased in CVD participants	[13]
AGEs	LC coupled with MS, ELISA	AGE/RAGE axis is correlated with CAD	[96]
Fatty acid metabolites	GC-MS, LC-MS, NMR Spectroscopy	Lipid-based metabolites associated with CVD	[97]
Itaconate	MS	Low risk of cholesterol-induced inflammation and atherosclerosis	[94,189]
Transcriptomics			
miR-21	qRT-PCR microarrays and sequencing approach	miR-21 is a regulator of cardiac diseases	[98,99]
miR-126	qRT-PCR microarrays and sequencing approach	Downregulated expression of miR - 126 associated with CVD	[100]
miR-155	qRT-PCR microarrays and sequencing approach	MiRNA-155 expression linked with cardiac death	[147]
miR-208a	qRT-PCR microarrays and sequencing approach	Linked to cardiac hypertrophy and heart failure	[190]
Long non-coding RNAs (lncRNAs)	qRT-PCR microarrays and sequencing approach	Emerging roles in CVD pathogenesis	[191]
Epigenomics			
DNA methylation (CpG sites)	MSP, MeDIP, RRBS, WGBS	CpG methylation associated with CVD development	[101]
Histone modifications	ChIP, ChIP-seq, ChIP - qPCR WB, IF, MS	Abnormal methylation promotes CVD	[102]

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Table 6 (*continued*)

Index	Research tools	Interpretation/Rational	Ref
MicroRNA methylation	MeRIP or MeRIP-seq, SCARLET-seq, RNA Sequencing Technologies, LC-MS/MS, Northern Blotting and Immunoblotting	miRNAs regulate CVD development	[103]
Non-coding RNA modifications	MeRIP, SCARLET-seq, Enzymatic Mapping, Northern Blotting and Immunoblotting, LC-MS/MS, Direct RNA Sequencing Technologies	Modifications in RNA bases, contribute to the progression of CVD	[104]
Metagenomics			
Inflammatory Microbiota	Microbiota/Metagenomic tools	The gut microbiota influence CVD risk through a pro-inflammatory effect	[105]
Ruminococcus	Microbiota/Metagenomic tools	Reduced abundance of *Ruminococcus* associated with CVD	[106]
Akkermansia	Microbiota/Metagenomic tools	*Akkermansia* associated with reduced aortic atherosclerosis	[107]
Prevotella	Microbiota/Metagenomic tools	*Alloprevotella* associated with decreased CVD risk/*Prevotella* 2 and *Prevotella* 7 associated with increased CVD risk	[192]
Bacteroides	Microbiota/Metagenomic tools	*Bacteroides* is a diagnostic marker in CAD patients	[148]
Lactobacillus	Microbiota/Metagenomic tools	*Lactobacillus plantarum* associated with reduced CVD risk	[193]

AGEs, Advanced glycation end products; BCAAs, Branched-chain amino acids; BNP, B-type natriuretic peptide; CAD, Coronay Artery Disease; Carotid IMT - carotid intima-media thickness; ChIP, Chromatin Immunoprecipitation; CLIA, Chemiluminescent Immunoassay; CRP, C-reactive protein; ELISA, Enzyme-Linked Immunosorbent Assay; GC – MS, Gas Chromatography-Mass Spectrometry; hsTnT, High-sensitivity Troponin T assay; IF, Immunofluorescence; LC MS, Liquid Chromatography-Mass Spectrometry; MeDIP, Methylated DNA Immunoprecipitation; MeRIP, Methylated RNA Immunoprecipitation; MMPs, Matrix metalloproteinases; MPO - Myeloperoxidase; MS, Mass Spectrometry; MSP, Methylation-Specific PCR; NMR, Nuclear Magnetic Resonance; oxLDL, Oxidized LDL; PAD, Peripheral Artery Disease; PCR, Polymerase chain reaction; qRT PCR, Quantitative Reverse Transcription Polymerase Chain Reaction; RRBS, Reduced Representation Bisulfite Sequencing; SCARLET-seq, Site-Specific Chemical Labeling Followed by RNA Sequencing; TMAO, Trimethylamine N-Oxide; WB, Western Blotting; WGBS, Whole-Genome Bisulfite Sequencing.

bolic, and phenotypic data to provide highly specific dietary guidance [108,128]. This strategy aims to optimize the measuring health outcomes by adapting the diet to an individual's biological and physiological needs [108]. The primary objective of these approaches is to screen the effectiveness of dietary and other lifestyle interventions to improve health and to prevent diseases such as cardiovascular disease, diabetes and obesity by considering the complexity of individual responses to different macronutrients [128], however, further advances and integrative bioinformatics tools are needed for clinical implementation.

To effectively understand and implement personalized and precise endogenous and exogenous determinants and individualized prescriptions and counseling, objective and global tools are essential [129]. These instruments include genomic testing, which analyzes an individual's DNA to identify genetic variants that affect nutrient metabolism and nutritional needs [130]. Metabolomics and proteomics provide insights into metabolic and molecular protein profiles, revealing real-time responses to dietary intake [131,132]. Microbiome analysis also examines the composition of gut bacteria that influence digestion and health [133,134]. In addition, digital health technologies, such as wearable devices and mobile apps, track dietary intake, physical activity and biomarkers, providing continuous feedback and data integration, benefit from data available. Together, these tools provide a comprehensive picture of an individual's health [135]. In addition, in precision nutrition, machine learning (ML) and artificial intelligence (AI) are pivotal in analyzing complex data sets to generate personalized dietary recommendations [136]. ML algorithms are able to detect subtle relationships within data that traditional statistical methods might miss, enabling more accurate predictions about interindividual differences to metabolize nutrients and respond to dietary changes interventions prescriptions [137]. On the other hand, AI tools also facilitate the integration of multi-omics data, providing a holistic view of individual health and allowing for the development of highly tailored nutritional interventions [137]. As a result, these technologies may improve the accuracy of dietary recommendations and medical therapies to prevent chronic diseases [136,137].

Traditional risk factors, including age, obesity, hypertension, diabetes, cholesterol levels, and lifestyle choices, remain critical in assessing CVD risk [2] Actually, CVD risk is influenced by a combination of non-modifiable and modifiable factors. Older age and mostly male sex are unmodifiable factors associated with increased CVD risk [138] which need to be addressed concurrently and objectively. Family background is also crucial as it is associated with recurrent cardiovascular events [48], while inherited anthropometric measures provide essential insights into CVD risk. Higher BMI is associated with increased CVD risk [49]. Similarly, greater waist circumference and waist to height ratio, measured by fat mass thickness, abdominal thickness, somatic measurements, and height measurement ratio, are indicative of higher CVD risk [50,51]. The fat mass index is another critical marker associated with CVD as well as body fat and muscle mass [52]. Moreover, lifestyle factors play a crucial role in CVD risk management, as sedentary habits, monitored via self-report questionnaires and activity monitors, are associated with an increased risk of CVD, especially with long-term sedentary behavior [53]. In addition, dietary intake of vitamin C, specific carotenoids (β-carotene, lycopene) and α-tocopherol (as markers of fruit and vegetable intake) which are basic components of the Mediterranean diet, are associated lower risk of coronary heart disease, stroke and CVD overall [54](58). Within this scope, the PREDIMED and the CORDIOPREV studies demonstrated that a high-unsaturated fat and (poly)phenol-rich dietary pattern such as the Mediterranean diet are useful tool in the prevention of CVD [139,140]. Similarly, smoking is a well-known risk factor for coronary heart disease [55] (59). Stress and loneliness [141], measured through various psychological and physiological tools, contributes to atherogenesis and CVD risk [56]. Lastly, alcohol abuse [142] or low essential fatty acid intakes [143,144] are associated with increased CVD risk. Early assessment of liver disease in obese patients is essential to establish cardiovascular risk [145,146]. In short, promoting a healthy lifestyle is the most important cardiopreventive measure that can and should be implemented.

In addition to the aforementioned, it is important to underscore that the integration of omics markers is revolutionizing our understanding of CVD risk and management [135]. In genomics, specific genetic variants such as *SORT1* and *CDKN2A/2B* have been associated with cholesterol levels and coronary artery disease risk using tools such as genotyping arrays [130] (163). Further, *CELSR2-PSRC1-SORT1* and *FADS1* were associated with CVD and coronary heart disease, respectively [85,86] whereas *LPA* was inversely associated with carotid intima-media thickness [87]. Moreover, proteomic markers, including troponin T and BNP, have been identified as biomarkers of myocardial infarction and stroke risk and are associated with classical CVD factors [88,89]. Metabolomic studies highlight the role of metabolites like TMAO and oxLDL in CVD, while demonstrating the significant role of AGEs. Furthermore, transcriptomic markers, including miR-21 and miR-155, are regulators of cardiac disease and manifest an emerging role in CVD pathogenesis [98,99,147]. Epigenomic factors such as DNA

methylation and histone modifications, also play a significant role in CVD development showing that abnormal methylation can lead to cardiometabolic abnormalities [101,102]. Along with, metagenomic analysis reveals that gut microbiota, such as *Akkermansia* and *Bacteroides*, influence cardiovascular risk through proinflammatory effects [107,148], but some other bacteria, such as *Ruminococcus* and other ones have protective roles [106,149,150]. Thus, this comprehensive multi-omics approach provides actionable insights into pathogenesis and the therapeutic approach of CVD.

5. Conclusion and perspectives

Personalized and precision medicine and nutrition are innovative strategies tailored to an individuals' unique genetic, lifestyle, and health profile, aiming to optimize health outcomes and prevent diseases such as CVD, diabetes, and obesity [125,126]. Traditional risk factors mentioned above, are identified in landmark studies such as the Framingham Heart Study, have been incorporated into various risk prediction models such as SCORE, REYNOLDS RISK SCORE, and ASCVD [40]. Moreover, the integration of "omics" markers like genomic, proteomic, metabolomic, epigenomic, transcriptomic, epigenomic and metagenomic markers is providing deeper insights into the molecular basis of CVD [42,135].

The use of advanced tools like genomic testing, metabolomics, proteomics, microbiome analysis, and digital health technologies improves the accuracy of dietary recommendations and aids in the prevention and management of chronic diseases [42]. Furthermore, the application of machine learning and artificial intelligence in precision nutrition enables the analysis of complex datasets and the generation of highly tailored dietary recommendations [136,137].

In conclusion, a comprehensive approach that integrates traditional risk factors with advanced omics data science and risk scores should and will provide a robust framework for better understanding and managing CVD better. Indeed, given the multifactorial etiology of CVD and the interaction between risk factors, there is no single biomarker able to explain alone the measurable risks, neither the residual nor the excess of risk found in CVD, that health professionals need to be aware of the overall tools that are critical for clinical practice or research endeavors. Therefore, these newer holistic tools will facilitate personalized risk stratification, guide clinical decision-making and preventive strategies to mitigate CVD risk, ultimately individualize patient prescriptions and outcomes, implement public health policies and promote tailored measurement for precision information of personalized medicine/nutrition.

Patient consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Authors' contributions

Conceptualization DMU, JAM, SG, FVO. Extensive bibliography search: DMU, SG, FVO, AHH, MFLA, BV, ORL. Complementary bibliography search: all authors. Graphical material: FVO, JAM, DMU, and SG. Critical revision of the final version: all authors. Coordination and corresponding authors' duties: JAM, ORL, MY, FVO, SG.

Ethics approval and consent to participate

Not applicable.

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References

[1] Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. J Am Coll Cardiol 2019;74:2529–32.
[2] Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk: a compass for future health. J Am Coll Cardiol 2022;80:2361–71.
[3] Matza LS, Stewart KD, Gandra SR, Delio PR, Fenster BE, Davies EW, et al. Acute and chronic impact of cardiovascular events on health state utilities. BMC Health Serv Res 2015;15:173.
[4] Klingel R, Heibges A, Fassbender C, ProLiFe-Study G. Prevention of cardiovascular complications in patients with Lp(a)-hyperlipoproteinemia and progressive cardiovascular disease by long-term lipoprotein apheresis according to German national guidelines. Clin Res Cardiol Suppl 2017;12:38–43.
[5] Juarez PD, Hood DB, Song MA, Ramesh A. Use of an exposome approach to understand the effects of exposures from the natural, built, and social environments on cardio-vascular disease onset, progression, and outcomes. Front Public Health 2020;8:379.
[6] Fruchart JC, Sacks FM, Hermans MP, Assmann G, Brown WV, Ceska R, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in dyslipidaemic patient. Diabetes Vasc Dis Res 2008;5:319–35.
[7] Guallar E, Banegas JR, Blasco-Colmenares E, Jimenez FJ, Dallongeville J, Halcox JP, et al. Excess risk attributable to traditional cardiovascular risk factors in clinical practice settings across Europe - the EURIKA Study. BMC Public Health 2011;11:704.
[8] Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38:2459–72.
[9] Miao B, Hernandez AV, Alberts MJ, Mangiafico N, Roman YM, Coleman CI. Incidence and predictors of major adverse cardiovascular events in patients with established atherosclerotic disease or multiple risk factors. J Am Heart Assoc 2020;9:e014402.
[10] Venkataramani R, Lewis AE, Santos JI, Dhondu HS, Ramakrishna H. Maternal and fetal outcomes in adult congenital heart disease. J Cardiothorac Vasc Anesth 2022;36:3676–84.
[11] Schaefer EJ, Asztalos BF, Vaisar T, Diffenderfer MR, Brewer Jr HB, Stock EO, et al. High density lipoprotein particle composition, functionality, deficiency, and atherosclerotic cardiovascular disease risk: a review. Curr Atheroscler Rep 2025;27:62.
[12] Tall AR, Thomas DG, Gonzalez-Cabodevilla AG, Goldberg IJ. Addressing dyslipidemic risk beyond LDL-cholesterol. J Clin Investig 2022;132.
[13] Hong CG, Florida E, Li H, Parel PM, Mehta NN, Sorokin AV. Oxidized low-density lipoprotein associates with cardiovascular disease by a vicious cycle of atherosclerosis and inflammation: a systematic review and meta-analysis. Front Cardiovasc Med 2022;9:1023651.
[14] Li N. Platelets as an inter-player between hyperlipidaemia and atherosclerosis. J Intern Med 2024;296:39–52.
[15] Motairek I, Makhlouf MHE, Rajagopalan S, Al-Kindi S. The exposome and cardiovascular health. Can J Cardiol 2023;39:1191–203.
[16] Trovato FM, Zia R, Artru F, Mujib S, Jerome E, Cavazza A, et al. Lysophosphatidylcholines modulate immunoregulatory checkpoints in peripheral monocytes and are associated with mortality in people with acute liver failure. J Hepatol 2023;78:558–73.
[17] Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 2010;72:219–46.
[18] DeBord DG, Carreon T, Lentz TJ, Middendorf PJ, Hoover MD, Schulte PA. Use of the "exposome" in the practice of epidemiology: a primer on -omic technologies. Am J Epidemiol 2016;184:302–14.
[19] Munzel T, Sorensen M, Hahad O, Nieuwenhuijsen M, Daiber A. The contribution of the exposome to the burden of cardiovascular disease. Nat Rev Cardiol 2023;20:651–69.
[20] Zhang P, Carlsten C, Chaleckis R, Hanhineva K, Huang M, Isobe T, et al. Defining the scope of exposome studies and research needs from a multidisciplinary perspective. Environ Sci Technol Lett 2021;8:839–52.
[21] Del Saz-Lara A, Lopez de Las Hazas MC, Visioli F, Davalos A. Nutri-epigenetic effects of phenolic compounds from extra virgin olive oil: a systematic review. Adv Nutr 2022;13:2039–60.
[22] Foster D, Sanchez-Collins S, Cheskin LJ. Erratum: multidisciplinary team-based obesity treatment in patients with diabetes: current practices and the state of the science. Diabetes Spectr 2017;30:244–9. https://doi.org/10.2337/ds17-0045. Diabetes Spectr. 2018;31:119.
[23] Foster D, Sanchez-Collins S, Cheskin LJ. Multidisciplinary team-based obesity treatment in patients with diabetes: current practices and the state of the science. Diabetes Spectr 2017;30:244–9.

[24] Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al. American association of clinical endocrinologists and American college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr Pract 2016;22(Suppl 3):1–203.
[25] Cox N, Crozet L, Holtman IR, Loyher PL, Lazarov T, White JB, et al. Diet-regulated production of PDGFcc by macrophages controls energy storage. Science 2021;373.
[26] Sitinjak BDP, Murdaya N, Rachman TA, Zakiyah N, Barliana MI. The potential of single nucleotide polymorphisms (SNPs) as biomarkers and their association with the increased risk of coronary heart disease: a systematic review. Vasc Health Risk Manag 2023;19:289–301.
[27] Vrablik M, Dlouha D, Todorovova V, Stefler D, Hubacek JA. Genetics of cardiovascular disease: how far are we from personalized CVD risk prediction and management? Int J Mol Sci 2021;22.
[28] Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med 2016; 375:2349–58.
[29] Hajar R. Genetics in cardiovascular disease. Heart Views 2020;21:55–6.
[30] Mach F, Visseren FLJ, Cater NB, Salhi N, Soronen J, Ray KK, et al. Addressing residual risk beyond statin therapy: new targets in the management of dyslipidaemias-A report from the European Society of Cardiology Cardiovascular Round Table. J Clin Lipidol 2024;18:e685–700.
[31] Fruchart JC, Nierman MC, Stroes ES, Kastelein JJ, Duriez P. New risk factors for atherosclerosis and patient risk assessment. Circulation 2004;109:III15-IIII19.
[32] Reijnders E, van der Laarse A, Jukema JW, Cobbaert CM. High residual cardiovascular risk after lipid-lowering: prime time for Predictive, Preventive, Personalized, Participatory, and Psycho-cognitive medicine. Front Cardiovasc Med 2023;10:1264319.
[33] Wong ND, Zhao Y, Quek RGW, Blumenthal RS, Budoff MJ, Cushman M, et al. Residual atherosclerotic cardiovascular disease risk in statin-treated adults: the Multi-Ethnic Study of Atherosclerosis. J Clin Lipidol 2017;11:1223–33.
[34] Siniawski D, Masson G, Masson W, Barbagelata L, Destaville J, Lynch S, et al. Residual cardiovascular risk, use of standard care treatments, and achievement of treatment goals in patients with cardiovascular disease. Int J Cardiol Cardiovasc Risk Prev 2023;18:200198.
[35] Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73–8.
[36] Califf RM. Biomarker definitions and their applications. Exp Biol Med (Maywood) 2018;243:213–21.
[37] Griffiths HR, Moller L, Bartosz G, Bast A, Bertoni-Freddari C, Collins A, et al. Biomarkers. Mol Aspects Med 2002;23:101–208.
[38] Kim SJ, Mesquita FCP, Hochman-Mendez C. New biomarkers for cardiovascular disease. Tex Heart Inst J 2023;50.
[39] Hajar R. Risk factors for coronary artery disease: historical perspectives. Heart Views 2017;18:109–14.
[40] Sofogianni A, Stalikas N, Antza C, Tziomalos K. Cardiovascular risk prediction models and scores in the era of personalized medicine. J Pers Med 2022;12.
[41] Gunaydin ZY, Karagoz A, Bektas O, Kaya A, Kiris T, Erdogan G, et al. Comparison of the Framingham risk and SCORE models in predicting the presence and severity of coronary artery disease considering SYNTAX score. Anatol J Cardiol 2016;16:412–8.
[42] Leon-Mimila P, Wang J, Huertas-Vazquez A. Relevance of multi-omics studies in cardiovascular diseases. Front Cardiovasc Med 2019;6:91.
[43] Lv J, Pan C, Cai Y, Han X, Wang C, Ma J, et al. Plasma metabolomics reveals the shared and distinct metabolic disturbances associated with cardiovascular events in coronary artery disease. Nat Commun 2024;15:5729.
[44] Siurana JM, Sabate-Rotes A, Amigo N, Martinez-Micaelo N, Arciniegas L, Riaza L, et al. Different profiles of lipoprotein particles associate various degrees of cardiac involvement in adolescents with morbid obesity. Front Pediatr 2022;10: 887771.
[45] Konig IR, Fuchs O, Hansen G, von Mutius E, Kopp MV. What is precision medicine? Eur Respir J 2017;50.
[46] Filipovic MG, Luedi MM. Cardiovascular biomarkers: current status and future directions. Cells 2023;12.
[47] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[48] Wahrenberg A, Kuja-Halkola R, Magnusson PKE, Habel H, Warnqvist A, Hambraeus K, et al. Cardiovascular family history increases the risk of disease recurrence after a first myocardial infarction. J Am Heart Assoc 2021;10:e022264.
[49] Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, et al. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. JAMA Cardiol 2018;3:280–7.
[50] Xue R, Li Q, Geng Y, Wang H, Wang F, Zhang S. Abdominal obesity and risk of CVD: a dose-response meta-analysis of thirty-one prospective studies. Br J Nutr 2021;126:1420–30.
[51] Shen S, Lu Y, Qi H, Li F, Shen Z, Wu L, et al. Waist-to-height ratio is an effective indicator for comprehensive cardiovascular health. Sci Rep 2017;7:43046.
[52] Yamashita K, Kondo T, Osugi S, Shimokata K, Maeda K, Okumura N, et al. The significance of measuring body fat percentage determined by bioelectrical impedance analysis for detecting subjects with cardiovascular disease risk factors. Circ J 2012;76:2435–42.
[53] Liang ZD, Zhang M, Wang CZ, Yuan Y, Liang JH. Association between sedentary behavior, physical activity, and cardiovascular disease-related outcomes in adults-A meta-analysis and systematic review. Front Public Health 2022;10: 1018460.
[54] Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, et al. Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies. Am J Clin Nutr 2018;108: 1069–91.
[55] Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. Eur Heart J 2005;26:1765–73.
[56] Roemmich JN, Lambiase MJ, Balantekin KN, Feda DM, Dorn J. Stress, behavior, and biology: risk factors for cardiovascular diseases in youth. Exerc Sport Sci Rev 2014;42:145–52.
[57] Poli A, Marangoni F, Avogaro A, Barba G, Bellentani S, Bucci M, et al. Moderate alcohol use and health: a consensus document. Nutr Metabol Cardiovasc Dis 2013; 23:487–504.
[58] Iatan I, Koschinsky ML, Trenaman L, Zhang W, Thanassoulis G, Brunham LR, et al. Rationale for the routine screening of lipoprotein (a) in cardiovascular risk assessment. Eur J Prev Cardiol 2025.
[59] Torossian A, Genoux A, Cai Z, Jolivet N, Croyal M, Oliveira AR, et al. Plasma apolipoprotein concentrations and occurrence of cardiovascular events in the general population: an exploratory analysis. Atheroscler Plus 2025;60:35–42.
[60] Ademovic E, Cakaric M, Durak-Nalbantic A, Dzubur A, Hodzic E, Mahmutovic S, et al. Triglyceride level as a potential marker of residual cardiovascular risk and its relation to HeartScore. Technol Health Care 2023;31:2145–53.
[61] Feng M, Sun T, Zhao Y, Zhang H. Detection of serum interleukin-6/10/18 levels in sepsis and its clinical significance. J Clin Lab Anal 2016;30:1037–43.
[62] Yuan S, Carter P, Bruzelius M, Vithayathil M, Kar S, Mason AM, et al. Effects of tumour necrosis factor on cardiovascular disease and cancer: a two-sample Mendelian randomization study. EBioMedicine 2020;59:102956.
[63] Jenny NS, Arnold AM, Kuller LH, Sharrett AR, Fried LP, Psaty BM, et al. Soluble intracellular adhesion molecule-1 is associated with cardiovascular disease risk and mortality in older adults. J Thromb Haemostasis 2006;4:107–13.
[64] Khan AA, Alsahli MA, Rahmani AH. Myeloperoxidase as an active disease biomarker: recent biochemical and pathological perspectives. Med Sci 2018;6.
[65] Troncoso MF, Ortiz-Quintero J, Garrido-Moreno V, Sanhueza-Olivares F, Guerrero-Moncayo A, Chiong M, et al. VCAM-1 as a predictor biomarker in cardiovascular disease. Biochim Biophys Acta Mol Basis Dis 2021;1867:166170.
[66] Liu JR, Liu Y, Yin FZ, Liu BW. Serum ferritin, an early marker of cardiovascular risk: a study in Chinese men of first-degree relatives with family history of type 2 diabetes. BMC Cardiovasc Disord 2019;19:82.
[67] Kosmas CE, Bousvarou MD, Kostara CE, Papakonstantinou EJ, Salamou E, Guzman E. Insulin resistance and cardiovascular disease. J Int Med Res 2023;51: 3000605231164548.
[68] Perpetuo L, Voisin PM, Amado F, Hirtz C, Vitorino R. Ghrelin and adipokines: an overview of their physiological role, antimicrobial activity and impact on cardiovascular conditions. Vitam Horm 2021;115:477–509.
[69] Vilarino-Garcia T, Polonio-Gonzalez ML, Perez-Perez A, Ribalta J, Arrieta F, Aguilar M, et al. Role of leptin in obesity, cardiovascular disease, and type 2 diabetes. Int J Mol Sci 2024;25.
[70] Shaye K, Amir T, Shlomo S, Yechezkel S. Fasting glucose levels within the high normal range predict cardiovascular outcome. Am Heart J 2012;164:111–6.
[71] Pletsch-Borba L, Grafetstatter M, Husing A, Gonzalez Maldonado S, Kloss M, Gross ML, et al. Author Correction: biomarkers of vascular injury in relation to myocardial infarction risk: a population-based study. Sci Rep 2019;9:8037.
[72] Pletsch-Borba L, Grafetstatter M, Husing A, Gonzalez Maldonado S, Kloss M, Gross ML, et al. Biomarkers of vascular injury in relation to myocardial infarction risk: a population-based study. Sci Rep 2019;9:3004.
[73] Echouffo-Tcheugui JB, Zhang S, Daya N, McEvoy JW, Tang O, Juraschek SP, et al. NT-proBNP and all-cause and cardiovascular mortality in us adults: a prospective cohort study. J Am Heart Assoc 2023;12:e029110.
[74] Szpakowicz A, Szpakowicz M, Lapinska M, Paniczko M, Lawicki S, Raczkowski A, et al. Serum chemerin concentration is associated with proinflammatory status in chronic coronary syndrome. Biomolecules 2021;11.
[75] Surma S, Banach M. Fibrinogen and atherosclerotic cardiovascular diseases-review of the literature and clinical studies. Int J Mol Sci 2021;23.
[76] Akgul O, Uyarel H. D-dimer: a novel predictive marker for cardiovascular disease. Int J Cardiol 2013;168:4930–1.
[77] Ng C, Motto DG, Di Paola J. Diagnostic approach to von Willebrand disease. Blood 2015;125:2029–37.
[78] Mohamed SF, Khayeka-Wandabwa C, Muthuri S, Ngomi NN, Kyobutungi C, Haregu TN. Carotid intima media thickness (CIMT) in adults in the AWI-Gen Nairobi site study: profiles and predictors. Hipertens Riesgo Vasc 2023;40:5–15.
[79] Obisesan OH, Osei AD, Uddin SMI, Dzaye O, Blaha MJ. An update on coronary artery calcium interpretation at chest and cardiac CT. Radiol Cardiothorac Imag 2021;3:e200484.
[80] Maruhashi T, Kajikawa M, Kishimoto S, Yamaji T, Harada T, Hashimoto Y, et al. The prevalence of cardiovascular disease is higher in patients with bilateral low ankle-brachial index than in patients with unilateral low ankle-brachial index. Atherosclerosis 2022;360:8–14.
[81] Graham IM, Di Angelantonio E, Visseren F, De Bacquer D, Ference BA, Timmis A, et al. Systematic coronary risk evaluation (SCORE): JACC focus seminar 4/8. J Am Coll Cardiol 2021;77:3046–57.
[82] Klisic A, Kavaric N, Bjelakovic B, Jovanovic M, Zvrko E, Stanisic V, et al. Cardiovascular risk assessed by Reynolds risk score in relation to waist circumference in apparently healthy middle-aged population in Montenegro. Acta

Clin Croat 2018;57:22–30.
[83] Xu LB, Zhang YQ, Zhang NN, Li B, Weng JY, Li XY, et al. Rs10757274 gene polymorphisms in coronary artery disease: a systematic review and a meta-analysis. Medicine (Baltim) 2020;99:e18841.
[84] Dutta A, Henley W, Lang IA, Murray A, Guralnik J, Wallace RB, et al. The coronary artery disease-associated 9p21 variant and later life 20-year survival to cohort extinction. Circ Cardiovasc Genet 2011;4:542–8.
[85] Castillo-Avila RG, Gonzalez-Castro TB, Tovilla-Zarate CA, Martinez-Magana JJ, Lopez-Narvaez ML, Juarez-Rojop IE, et al. Association between genetic variants of CELSR2-PSRC1-SORT1 and cardiovascular diseases: a systematic review and meta-analysis. J Cardiovasc Dev Dis 2023;10.
[86] Huang Y, Zhou J, Ye H, Xu L, Le Y, Yang X, et al. Relationship between chemokine (C-X-C motif) ligand 12 gene variant (rs1746048) and coronary heart disease: case-control study and meta-analysis. Gene 2013;521:38–44.
[87] Zabalza M, Subirana I, Lluis-Ganella C, Sayols-Baixeras S, de Groot E, Arnold R, et al. Association between coronary artery disease genetic variants and subclinical atherosclerosis: an association study and meta-analysis. Rev Esp Cardiol 2015;68:869–77.
[88] Golino M, Marazzato J, Blasi F, Morello M, Chierchia V, Cadonati C, et al. High-sensitivity cardiac troponin T and the diagnosis of cardiovascular disease in the emergency room: the importance of combining cardiovascular biomarkers with clinical data. J Clin Med 2022;11.
[89] Liu X, Abudukeremu A, Yu P, Cao Z, Sun R, Wu M, et al. Usefulness of B-type natriuretic peptide for predicting the risk of stroke in patients with heart failure with preserved ejection fraction. J Am Heart Assoc 2022;11:e024302.
[90] Fu Y, Wu Y, Liu E. C-reactive protein and cardiovascular disease: from animal studies to the clinic. Exp Ther Med 2020;20:1211–9 (Review).
[91] Nicholls SJ, Hazen SL. Myeloperoxidase and cardiovascular disease. Arterioscler Thromb Vasc Biol 2005;25:1102–11.
[92] Roncal C, Martinez-Aguilar E, Orbe J, Ravassa S, Fernandez-Montero A, Saenz-Pipaon G, et al. Trimethylamine-N-Oxide (TMAO) predicts cardiovascular mortality in peripheral artery disease. Sci Rep 2019;9:15580.
[93] Hong SH, Jang HH, Lee SR, Lee KH, Woo JS, Kim JB, et al. Impact of lysophosphatidylcholine on survival and function of UEA-1(+)acLDL (+) endothelial progenitor cells in patients with coronary artery disease. Heart Vessel 2015;30:115–25.
[94] Shan W, Cui J, Song Y, Yan D, Feng L, Jian Y, et al. Itaconate as a key player in cardiovascular immunometabolism. Free Radic Biol Med 2024;219:64–75.
[95] Wang Y, Huang K, Liu F, Lu X, Huang J, Gu D. Association of circulating branched-chain amino acids with risk of cardiovascular disease: a systematic review and meta-analysis. Atherosclerosis 2022;350:90–6.
[96] Fishman SL, Sonmez H, Basman C, Singh V, Poretsky L. The role of advanced glycation end-products in the development of coronary artery disease in patients with and without diabetes mellitus: a review. Mol Med 2018;24:59.
[97] McGranaghan P, Kirwan JA, Garcia-Rivera MA, Pieske B, Edelmann F, Blaschke F, et al. Lipid metabolite biomarkers in cardiovascular disease: discovery and biomechanism translation from human studies. Metabolites 2021;11.
[98] Surina Fontanella RA, Scisciola L, Marfella R, Paolisso G, Barbieri M. Corrigendum: miR-21 in human cardiomyopathies. Front Cardiovasc Med 2022;9:913429.
[99] Surina S, Fontanella RA, Scisciola L, Marfella R, Paolisso G, Barbieri M. miR-21 in human cardiomyopathies. Front Cardiovasc Med 2021;8:767064.
[100] Theofilis P, Oikonomou E, Vogiatzi G, Sagris M, Antonopoulos AS, Siasos G, et al. The role of MicroRNA-126 in atherosclerotic cardiovascular diseases. Curr Med Chem 2023;30:1902–21.
[101] Krolevets M, Cate VT, Prochaska JH, Schulz A, Rapp S, Tenzer S, et al. DNA methylation and cardiovascular disease in humans: a systematic review and database of known CpG methylation sites. Clin Epigenetics 2023;15:56.
[102] Yang Y, Luan Y, Yuan RX, Luan Y. Histone methylation related therapeutic challenge in cardiovascular diseases. Front Cardiovasc Med 2021;8:710053.
[103] Lopez-Pedrera C, Barbarroja N, Patino-Trives AM, Luque-Tevar M, Torres-Granados C, Aguirre-Zamorano MA, et al. Role of microRNAs in the development of cardiovascular disease in systemic autoimmune disorders. Int J Mol Sci 2020;21.
[104] Yang X, Gokulnath P, Lehmann HI, Hou Z, Yang S, You L, et al. RNA modifications in aging-associated cardiovascular diseases. Aging (Albany NY) 2022;14:8110–36.
[105] Nesci A, Carnuccio C, Ruggieri V, D'Alessandro A, Di Giorgio A, Santoro L, et al. Gut microbiota and cardiovascular disease: evidence on the metabolic and inflammatory background of a complex relationship. Int J Mol Sci 2023;24.
[106] Lakshmanan AP, Al Zaidan S, Bangarusamy DK, Al-Shamari S, Elhag W, Terranegra A. Increased relative abundance of ruminococcus is associated with reduced cardiovascular risk in an obese population. Front Nutr 2022;9:849005.
[107] Witkowski M, Weeks TL, Hazen SL. Gut microbiota and cardiovascular disease. Circ Res 2020;127:553–70.
[108] Wang DD, Hu FB. Precision nutrition for prevention and management of type 2 diabetes. Lancet Diabetes Endocrinol 2018;6:416–26.
[109] Salunke DD, Aher AA, Thitame SN. Endocrine disorder: advance in understanding diabetes and obesity A review. J Pharm BioAllied Sci 2025;17:S32–5.
[110] Muoio DM. Metabolic inflexibility: when mitochondrial indecision leads to metabolic gridlock. Cell 2014;159:1253–62.
[111] Visioli F, Ingram A, Beckman JS, Magnusson KR, Hagen TM. Strategies to protect against age-related mitochondrial decay: do natural products and their derivatives help? Free Radic Biol Med 2022;178:330–46.
[112] Peoples JN, Saraf A, Ghazal N, Pham TT, Kwong JQ. Mitochondrial dysfunction and oxidative stress in heart disease. Exp Mol Med 2019;51:1–13.
[113] Pliouta L, Lampsas S, Kountouri A, Korakas E, Thymis J, Kassi E, et al. Mitochondrial dysfunction in the development and progression of cardiometabolic diseases: a narrative review. J Clin Med 2025;14.
[114] Perrone A, Giovino A, Benny J, Martinelli F. Advanced glycation end products (AGEs): biochemistry, signaling, analytical methods, and epigenetic effects. Oxid Med Cell Longev 2020;2020:3818196.
[115] Uceda AB, Marino L, Casasnovas R, Adrover M. An overview on glycation: molecular mechanisms, impact on proteins, pathogenesis, and inhibition. Biophys Rev 2024;16:189–218.
[116] Dwivedi AK, Dubey P, Reddy SY, Clegg DJ. Associations of glycemic index and glycemic load with cardiovascular disease: updated evidence from meta-analysis and cohort studies. Curr Cardiol Rep 2022;24:141–61.
[117] Tome-Carneiro J, Visioli F. Plant-based diets reduce blood pressure: a systematic review of recent evidence. Curr Hypertens Rep 2023;25:127–50.
[118] de Oliveira Melo NC, Cuevas-Sierra A, Souto VF, Martinez JA. Biological rhythms, chrono-nutrition, and gut microbiota: epigenomics insights for precision nutrition and metabolic health. Biomolecules 2024;14.
[119] Hirschey MD, Shimazu T, Goetzman E, Jing E, Schwer B, Lombard DB, et al. SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. Nature 2010;464:121–5.
[120] Pougovkina O, te Brinke H, Ofman R, van Cruchten AG, Kulik W, Wanders RJ, et al. Mitochondrial protein acetylation is driven by acetyl-CoA from fatty acid oxidation. Hum Mol Genet 2014;23:3513–22.
[121] Watson N, Kuppuswamy S, Ledford WL, Sukumari-Ramesh S. The role of HDAC3 in inflammation: mechanisms and therapeutic implications. Front Immunol 2024;15:1419685.
[122] Fang Z, Wang X, Sun X, Hu W, Miao QR. The role of histone protein acetylation in regulating endothelial function. Front Cell Dev Biol 2021;9:672447.
[123] Ramos-Lopez O, Milton-Laskibar I, Martinez JA, Collaborators, Rodrigo S-C, Maria PP. Precision nutrition based on phenotypical traits and the (epi)genotype: nutrigenetic and nutrigenomic approaches for obesity care. Curr Opin Clin Nutr Metab Care 2021;24:315–25.
[124] Ramos-Lopez O, Assmann TS, Astudillo Munoz EY, Baquerizo-Sedano L, Barron-Cabrera E, Bernal CA, et al. Guidance and position of RINN22 regarding precision nutrition and nutriomics. Lifestyle Genom 2025;18:1–19.
[125] Ordovas JM, Ferguson LR, Tai ES, Mathers JC. Personalised nutrition and health. BMJ 2018;361. bmj k2173.
[126] What will it take to make precision health a global reality. Nat Med 2024;30:1793–4.
[127] Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. Cell 2015;163:1079–94.
[128] Collaborators GBDD. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019;393:1958–72.
[129] Livingstone K, Ramos López OO, Pérusse L, Kato H, Ordovas J, Alfredo M. Reprint of: precision nutrition: a review of current approaches and future endeavors. Trends Food Sci Technol 2022;130.
[130] O'Donnell CJ, Nabel EG. Genomics of cardiovascular disease. N Engl J Med 2011;365:2098–109.
[131] Li Y, Gray A, Xue L, Farb MG, Ayalon N, Andersson C, et al. Metabolomic profiles, ideal cardiovascular health, and risk of heart failure and atrial fibrillation: insights from the framingham heart study. J Am Heart Assoc 2023;12:e028022.
[132] Gong M, Zhang Y, Chen N, Ma LL, Feng XM, Yan YX. Proteomics in cardiovascular disease. Clin Chim Acta 2024;557:117877.
[133] Rahman MM, Islam F, Or-Rashid MH, Mamun AA, Rahaman MS, Islam MM, et al. The gut microbiota (microbiome) in cardiovascular disease and its therapeutic regulation. Front Cell Infect Microbiol 2022;12:903570.
[134] Scarmozzino F, Poli A, Visioli F. Microbiota and cardiovascular disease risk: a scoping review. Pharmacol Res 2020;159:104952.
[135] Doran S, Arif M, Lam S, Bayraktar A, Turkez H, Uhlen M, et al. Multi-omics approaches for revealing the complexity of cardiovascular disease. Brief Bioinform 2021;22.
[136] Sahu M, Gupta R, Ambasta RK, Kumar P. Artificial intelligence and machine learning in precision medicine: a paradigm shift in big data analysis. Prog Mol Biol Transl Sci 2022;190:57–100.
[137] MacEachern SJ, Forkert ND. Machine learning for precision medicine. Genome 2021;64:416–25.
[138] Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, et al. Cardiovascular risks associated with gender and aging. J Cardiovasc Dev Dis 2019;6.
[139] Ros E, Martinez-Gonzalez MA, Estruch R, Salas-Salvado J, Fito M, Martinez JA, et al. Mediterranean diet and cardiovascular health: teachings of the PREDIMED study. Adv Nutr 2014;5. 330S-6S.
[140] Delgado-Lista J, Alcala-Diaz JF, Torres-Pena JD, Quintana-Navarro GM, Fuentes F, Garcia-Rios A, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet 2022;399:1876–85.
[141] Bernardi E, Visioli F. Fostering wellbeing and healthy lifestyles through conviviality and commensality: underappreciated benefits of the Mediterranean Diet. Nutr Res 2024;126:46–57.
[142] Seth C, Schmid V, Mueller S, Haykowsky M, Foulkes SJ, Halle M, et al. Diabetes, obesity, and cardiovascular disease-what is the impact of lifestyle modification? Herz 2025.

[143] Visioli F, Poli A. Fatty acids and cardiovascular risk. Evidence, lack of evidence, and diligence. Nutrients 2020;12:1–19.
[144] Visioli F, Risè P, Plasmati E, Pazzucconi F, Sirtori CR, Galli C. Very low intakes of n-3 fatty acids incorporated into bovine milk reduce plasma triacylglycerol and increase HDL-cholesterol concentrations in healthy subjects. Pharmacol Res 2000; 41:571–6.
[145] Wang X, You J, Tang J, Li X, Wang R, Li Y, et al. Interaction between non-alcoholic fatty liver disease and obesity on the risk of developing cardiovascular diseases. Sci Rep 2024;14:24024.
[146] Simon TG, Roelstraete B, Hagstrom H, Sundstrom J, Ludvigsson JF. Non-alcoholic fatty liver disease and incident major adverse cardiovascular events: results from a nationwide histology cohort. Gut 2022;71:1867–75.
[147] Cao RY, Li Q, Miao Y, Zhang Y, Yuan W, Fan L, et al. The emerging role of MicroRNA-155 in cardiovascular diseases. BioMed Res Int 2016;2016:9869208.
[148] Tsai HJ, Tsai WC, Hung WC, Hung WW, Chang CC, Dai CY, et al. Gut microbiota and subclinical cardiovascular disease in patients with type 2 diabetes mellitus. Nutrients 2021;13.
[149] Salamat S, Tabandeh MR, Jahan-Mihan A, Mansoori A. The effect of supplementation with a multi-species synbiotic on serum lipid profile, abundance of beneficial gut bacteria and firmicutes to bacteroidetes ratio in patients with dyslipidemia; a randomized, double-blind, placebo-controlled, clinical trial. PharmaNutrition 2024;27.
[150] Porcari S, Ng SC, Zitvogel L, Sokol H, Weersma RK, Elinav E, et al. The microbiome for clinicians. Cell 2025;188:2836–44.
[151] Sacks FM, Campos H. Clinical review 163: cardiovascular endocrinology: low-density lipoprotein size and cardiovascular disease: a reappraisal. J Clin Endocrinol Metab 2003;88:4525–32.
[152] Emerging Risk Factors C, Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, et al. Lipid-related markers and cardiovascular disease prediction. JAMA 2012;307:2499–506.
[153] Armitage J, Holmes MV, Preiss D. Cholesteryl ester transfer protein inhibition for preventing cardiovascular events: JACC review topic of the week. J Am Coll Cardiol 2019;73:477–87.
[154] Koenig W, Twardella D, Brenner H, Rothenbacher D. Lipoprotein-associated phospholipase A2 predicts future cardiovascular events in patients with coronary heart disease independently of traditional risk factors, markers of inflammation, renal function, and hemodynamic stress. Arterioscler Thromb Vasc Biol 2006;26: 1586–93.
[155] Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small dense low-density lipoprotein as biomarker for atherosclerotic diseases. Oxid Med Cell Longev 2017;2017:1273042.
[156] Corsetti JP, Sparks CE, James RW, Bakker SJL, Dullaart RPF. Low serum paraoxonase-1 activity associates with incident cardiovascular disease risk in subjects with concurrently high levels of high-density lipoprotein cholesterol and C-reactive protein. J Clin Med 2019;8.
[157] Cheung MC, Brown BG, Marino Larsen EK, Frutkin AD, O'Brien KD, Albers JJ. Phospholipid transfer protein activity is associated with inflammatory markers in patients with cardiovascular disease. Biochim Biophys Acta 2006;1762:131–7.
[158] Law SH, Chan HC, Ke GM, Kamatam S, Marathe GK, Ponnusamy VK, et al. Untargeted lipidomic profiling reveals lysophosphatidylcholine and ceramide as atherosclerotic risk factors in apolipoprotein E knockout mice. Int J Mol Sci 2023; 24.
[159] Sotler T, Sebestjen M. PCSK9 as an atherothrombotic risk factor. Int J Mol Sci 2023;24.
[160] Bassuk SS, Rifai N, Ridker PM. High-sensitivity C-reactive protein: clinical importance. Curr Probl Cardiol 2004;29:439–93.
[161] Grammer TB, Scharnagl H, Dressel A, Kleber ME, Silbernagel G, Pilz S, et al. Iron metabolism, hepcidin, and mortality (the ludwigshafen risk and cardiovascular health study). Clin Chem 2019;65:849–61.
[162] van der Laan SW, Fall T, Soumare A, Teumer A, Sedaghat S, Baumert J, et al. Cystatin C and cardiovascular disease: a mendelian randomization study. J Am Coll Cardiol 2016;68:934–45.
[163] Vladu IM, Fortofoiu M, Clenciu D, Fortofoiu MC, Padureanu R, Radu L, et al. Insulin resistance quantified by the value of HOMA-IR and cardiovascular risk in patients with type 2 diabetes. Exp Ther Med 2022;23:73.
[164] Tao LC, Xu JN, Wang TT, Hua F, Li JJ. Triglyceride-glucose index as a marker in cardiovascular diseases: landscape and limitations. Cardiovasc Diabetol 2022;21: 68.
[165] Fernandez-Macias JC, Ochoa-Martinez AC, Varela-Silva JA, Perez-Maldonado IN. Atherogenic index of plasma: novel predictive biomarker for cardiovascular illnesses. Arch Med Res 2019;50:285–94.
[166] Rathi H, Kumar R, Goyal B, Kant R, Mirza AA, Rana S, et al. Assessment of dyslipidemia, lipid ratios, and atherogenic indices as cardiovascular risk factors in prediabetic and diabetic subjects. J Lab Physicians 2022;14:420–6.
[167] Kosmas CE, Rodriguez Polanco S, Bousvarou MD, Papakonstantinou EJ, Pena Genao E, Guzman E, et al. The triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio as a risk marker for metabolic syndrome and cardiovascular disease. Diagnostics (Basel) 2023;13.
[168] Walldius G, Jungner I. The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy--a review of the evidence. J Intern Med 2006;259:493–519.
[169] Lee HH, Lee HA, Kim EJ, Kim HY, Kim HC, Ahn SH, et al. Metabolic dysfunction-associated steatotic liver disease and risk of cardiovascular disease. Gut 2024;73:533–40.
[170] Zakerkish M, Hoseinian A, Alipour M, Payami SP. The Association between Cardio-metabolic and hepatic indices and anthropometric measures with metabolically obesity phenotypes: a cross-sectional study from the Hoveyzeh Cohort Study. BMC Endocr Disord 2023;23:122.
[171] Habib SS, Al-Khlaiwi T, Almushawah A, Alsomali A, Habib SA. Homocysteine as a predictor and prognostic marker of atherosclerotic cardiovascular disease: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2023;27: 8598–608.
[172] Somer S, Levy AP. The role of haptoglobin polymorphism in cardiovascular disease in the setting of diabetes. Int J Mol Sci 2020;22.
[173] Sibal L, Agarwal SC, Home PD, Boger RH. The role of asymmetric dimethylarginine (ADMA) in endothelial dysfunction and cardiovascular disease. Curr Cardiol Rev 2010;6:82–90.
[174] Egbuche O, Biggs ML, Ix JH, Kizer JR, Lyles MF, Siscovick DS, et al. Fatty acid binding protein-4 and risk of cardiovascular disease: the cardiovascular health study. J Am Heart Assoc 2020;9:e014070.
[175] Cheeseman J, Kuhnle G, Stafford G, Gardner RA, Spencer DI, Osborn HM. Sialic acid as a potential biomarker for cardiovascular disease, diabetes and cancer. Biomark Med 2021;15:911–28.
[176] Yano Y, Nakazato M, Toshinai K, Inokuchi T, Matsuda S, Hidaka T, et al. Circulating des-acyl ghrelin improves cardiovascular risk prediction in older hypertensive patients. Am J Hypertens 2014;27:727–33.
[177] van Trier TJ, Snaterse M, Boekholdt SM, Scholte Op, Reimer WJM, Hageman SHJ, Visseren FLJ, et al. Validation of systematic coronary risk evaluation 2 (SCORE2) and SCORE2-older persons in the EPIC-norfolk prospective population cohort. Eur J Prev Cardiol 2024;31:182–9.
[178] Sohn C, Kim J, Bae W. The framingham risk score, diet, and inflammatory markers in Korean men with metabolic syndrome. Nutr Res Prac 2012;6:246–53.
[179] Masson W, Siniawski D, Krauss J, Cagide A. [Clinical applicability of the framingham 30-year risk score. Usefulness in cardiovascular risk stratification and the diagnosis of carotid atherosclerotic plaque]. Rev Esp Cardiol 2011;64:305–11.
[180] Buitrago F, Canon-Barroso L, Diaz-Herrera N, Cruces-Muro E, Escobar-Fernandez M, Serrano-Arias JM. [Comparison of the REGICOR and SCORE function charts for classifying cardiovascular risk and for selecting patients for hypolipidemic or antihypertensive treatment]. Rev Esp Cardiol 2007;60:139–47.
[181] Guardino ET, Tarko L, Wilson PWF, Gaziano JM, Cho K, Gagnon DR, et al. Predictive value of ASCVD risk score for mortality and major adverse cardiovascular events in the year following a COVID-19 infection among US Veterans. Int J Cardiol 2023;387:131120.
[182] Preiss D, Kristensen SL. The new pooled cohort equations risk calculator. Can J Cardiol 2015;31:613–9.
[183] He Y, Li LW, Hao Y, Sim EY, Ng KL, Lee R, et al. Assessment of predictive validity and feasibility of Edmonton Frail Scale in identifying postoperative complications among elderly patients: a prospective observational study. Sci Rep 2020;10:14682.
[184] Hosein A, Stoute V, Chadee S, Singh NR. Evaluating Cardiovascular Disease (CVD) risk scores for participants with known CVD and non-CVD in a multiracial/ethnic Caribbean sample. PeerJ 2020;8:e8232.
[185] Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017;357:j2099.
[186] Palmieri L, Rielli R, Dematte L, Donfrancesco C, Ciccarelli P, De Sanctis Caiola P, et al. CUORE project: implementation of the 10-year risk score. Eur J Cardiovasc Prev Rehabil 2011;18:642–9.
[187] Pirs M, Jug B, Erzen B, Sabovic M, Karner P, Poljak M, et al. Cardiovascular risk assessment in HIV-infected male patients: a comparison of Framingham, SCORE, PROCAM and DAD risk equations. Acta Dermatovenerol Alp Pannonica Adriat 2014;23:43–7.
[188] Di Nubila A, Dilella G, Simone R, Barbieri SS. Vascular extracellular Matrix in atherosclerosis. Int J Mol Sci 2024;25.
[189] Cyr Y, Bozal FK, Barcia Duran JG, Newman AAC, Amadori L, Smyrnis P, et al. The IRG1-itaconate axis protects from cholesterol-induced inflammation and atherosclerosis. Proc Natl Acad Sci USA 2024;121:e2400675121.
[190] Huang XH, Li JL, Li XY, Wang SX, Jiao ZH, Li SQ, et al. miR-208a in cardiac hypertrophy and remodeling. Front Cardiovasc Med 2021;8:773314.
[191] Kohlmaier A, Holdt LM, Teupser D. Long noncoding RNAs in cardiovascular disease. Curr Opin Cardiol 2023;38:179–92.
[192] Kelly TN, Bazzano LA, Ajami NJ, He H, Zhao J, Petrosino JF, et al. Gut microbiome associates with lifetime cardiovascular disease risk profile among bogalusa heart study participants. Circ Res 2016;119:956–64.
[193] Naruszewicz M, Johansson ML, Zapolska-Downar D, Bukowska H. Effect of Lactobacillus plantarum 299v on cardiovascular disease risk factors in smokers. Am J Clin Nutr 2002;76:1249–55.