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## Innovations in Cardiovascular Disease Prevention: From Biomarkers to Digital Health Applications

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### Abstract

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, accounting for approximately 32% of all global deaths, and are responsible for about 45% of all deaths in Europe. CVD pathogenesis is characterized by complex interactions between genetic, environmental, and behavioral factors; important modifiable risk factors include smoking, obesity, a poor diet, and physical inactivity. This article examines the mechanisms underlying coronary artery disease (CAD) and atherosclerosis, including the roles of oxidative stress, inflammation, and adipocyte dysfunction. Atherosclerotic plaque formation, which is driven by high LDL levels, endothelial dysfunction, and oxidative stress, has been related to an increased risk of myocardial infarction and stroke. Furthermore, we discuss how systemic vasculitis, genetic and epigenetic factors, and microRNAs (miRNAs) such as miR-133a, miR-21, and miR-499a-5p regulate critical processes in smooth muscle cell proliferation and myocardial ischemia, emphasizing their dual potential as biomarkers and therapeutic targets. Early CVD diagnosis relies on novel biomarkers such as oxidized LDL, PAI-1, and CRP, especially in adolescent populations where obesity and metabolic syndrome contribute to disease onset. Prioritizing lifestyle factors such as food and exercise reduces the risk of cardiovascular disease in children and adolescents. Machine learning, poly-omic data integration, and digital health technologies can all be applied to personalized therapy and real-time cardiovascular risk assessment. Further study into multi-omic methods and the development of new biomarkers is needed for early detection and prevention among vulnerable populations.

**Keywords:** Cardiovascular diseases, Atherosclerosis, Inflammation, Proliferation, Myocardial ischemia.

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## Background

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels, including conditions such as coronary artery disease, cerebrovascular disease, rheumatic heart disease, and other heart and vascular disorders. According to Jagannathan et al. (2019), CVDs are the main cause of death worldwide due to their high morbidity and mortality rates. Risk factors for CVD are more prevalent in rural regions due to low screening and management rates. The three most common disorders in Europe are arterial hypertension (AH), coronary artery disease (CAD), and atherosclerosis. Cardiovascular diseases account for over 45% of all fatalities on the continent (Nowbar et al., 2019). Sub-Saharan Africa and Nigeria are expected to experience a sharp rise in cardiovascular disease (CVD)-related deaths (Yuyun et al., 2020). In Nigeria, ischemic heart disease and stroke are the two leading causes of CVD, accounting for around 10% of all fatalities (Nnate et al., 2021). Despite hypertension being a major risk factor, only 29% of people are aware of their hypertension status. In sub-Saharan Africa, heart failure, stroke, and hypertensive heart disease are the leading causes of CVD-related mortality, collectively accounting for over 55% of cardiovascular deaths in the region, while coronary artery disease (CAD) remains relatively rare (Minja et al., 2022). To address these concerns, the hospital infrastructure and other health policies should be enhanced. Atherosclerosis occurs when lipids, cholesterol, and inflammatory cells gradually accumulate in the arterial walls. According to Dhakal and Pokharel, (2024) coronary artery disease, or CAD, is defined as the narrowing or blockage of the coronary arteries, which lowers the heart's oxygen flow and raises the risk of heart attacks and sudden cardiac death. This disease's plaque formation can cause peripheral ischemia, myocardial infarction, or stroke by obstructing blood flow. Arterial hypertension is a common asymptomatic illness that destroys blood vessels and increases the risk of cardiovascular events such as heart failure and stroke (Frąk et al., 2022). CVDs have a complex etiology that are influenced by several non-modifiable characteristics such as age, gender, and inheritance. Lifestyle issues that can be changed include obesity, smoking, eating poorly, and not exercising. Rising obesity prevalence among young individuals contributes to the early development of CVD.

Atherosclerosis is primarily caused by high plasma cholesterol, specifically low-density lipoprotein (LDL), and the associated inflammatory response (Linton et al., 2019). This inflammation induces endothelial dysfunction by impairing nitric oxide production and increasing the expression of adhesion molecules, which facilitates the

infiltration of low-density lipoproteins (LDL) and immune cells into the arterial wall, promoting fat absorption and plaque formation (atherosclerosis). (Ubhenin et al., 2019) When coronary arteries constrict or block, the heart muscle receives less blood, increasing the risk of myocardial infarction or sudden cardiac death, as well as chest pain and ischemia (Shao et al., 2020). Arterial hypertension strains the vascular endothelium, causing structural changes leading to endothelial damage, and increased arterial stiffness, all of which contribute to heart failure and other cardiovascular disorders. The micro RNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression post-transcriptionally and play critical roles in cardiovascular physiology and pathology. Their stable presence in circulating blood and specific expression patterns associated with cardiovascular disease (CVD) make miRNAs promising biomarkers for early diagnosis, prognosis, and therapeutic monitoring of CVD (Kalayinia et al., 2021; Wronska, 2023). Changes in miRNA expression reflect underlying pathophysiological processes such as myocardial injury, inflammation, and vascular remodeling, enabling non-invasive detection and risk stratification in patients. However, challenges in clinical translation include variability in study findings, difficulties in standardizing detection methods, and the complexity of interpreting miRNA profiles in diverse patient populations (Moldovan et al., 2024). To overcome these barriers, advanced bioinformatics, and machine learning techniques have been increasingly applied to enhance miRNA target identification, validate biomarker panels, and facilitate the development of personalized therapeutic regimens tailored to individual molecular profiles (Natarajan et al., 2024). This study aims to build on these advances by systematically evaluating specific miRNAs as diagnostic and therapeutic biomarkers in CVD, contributing to precision cardiovascular medicine. Our understanding of cardiovascular pathophysiology is expanding to encompass thrombosis, insulin resistance, and adipocyte dysfunction (Petek & Varda, 2024). Despite its importance for blood artery integrity, hemostasis can become abnormal in CVD, resulting in thrombosis and increasing atherosclerosis. Recent technological advances have significantly enhanced the identification and management of cardiovascular disease (CVD). Biomarkers such as fibrinogen, PAI-1, and D-dimer are now being used to detect early cardiovascular risk in adolescents and young adults with obesity and metabolic disorders, enabling timely intervention (Kupčinskienė, 2018). In addition, innovations in metabolic medicines and regenerative therapies, including stem cell treatments and human-induced pluripotent stem cell-derived cardiomyocytes (HiPSC-CMs)—offer new insights into the molecular and cellular mechanisms underlying

CVD, paving the way for targeted therapeutic strategies (Narkar et al., 2022). Wearable technologies and continuous glucose monitoring (CGM) devices provide real-time physiological data, facilitating continuous risk assessment and personalized disease management. Despite these advances, the global burden of CVD remains high, underscoring the urgent need to discover novel biomarkers, elucidate biological pathways, and develop innovative therapies (Tardif et al., 2006). This study aims to address these gaps by integrating emerging biomarkers and cutting-edge technologies to improve early diagnosis and individualized treatment approaches in CVD, thereby contributing to precision cardiovascular medicine. This review critically evaluates recent advancements in novel biomarkers and digital health technologies to demonstrate their impact on enhancing early detection, personalized treatment, and management of cardiovascular disease, thereby aiming to reduce its global burden.

## Methodology

This review thoroughly examined recent improvements in cardiovascular disease (CVD) prevention, with a focus on biomarkers and digital health technology. A comprehensive literature search was undertaken in several leading scientific databases—Web of Science, PubMed, and Scopus—selected for their extensive coverage of biomedical, clinical, and interdisciplinary research relevant to digital health, biomarkers, and cardiovascular diseases (CVDs). Studies on microRNAs, oxidized LDL, PAI-1, CRP, and wearable technology were chosen due to their importance in early detection, CVD prevention, and novel treatment approaches. Data was gathered from reviews, epidemiological studies, and clinical trials to investigate the diagnostic and prognostic value of various biomarkers and technologies, as well as their application in high-risk and pediatric populations.

Digital health technology such as wearables, continuous glucose monitoring (CGM), and machine learning were also used to assess cardiovascular risk in real-time and adapt treatments. Clinical outcomes and diagnostic accuracy of various biomarkers and technologies were assessed using statistical analyses such as sensitivity, specificity, and receiver operating characteristic (ROC) curves, which provide a valuable tool for evaluating predictive performance. Although ROC curve analyses were not consistently reported across all included studies, their integration represents a promising trend for future research to enhance the precision of cardiovascular disease diagnostics. The Cochrane Risk of Bias tool and the GRADE framework were reliable methods for evaluating the quality of the included research. The exclusion of non-

English publications, while necessary to ensure consistency in data interpretation and quality assessment, may limit the comprehensiveness of our findings by potentially overlooking valuable insights and innovative strategies in cardiovascular disease (CVD) prevention reported in other languages.

## The pathology of coronary heart disease and atherosclerosis

Atherosclerosis and coronary artery disease (CAD) are closely related cardiovascular diseases defined by high-fat plaque formation and ongoing wall inflammation (Frak et al., 2022). These diseases account for the vast majority of morbidity and mortality worldwide. Oxidative stress, inflammation, endothelial dysfunction, and lipid buildup are all contributing factors in the development of atherosclerosis and CAD (Ubhenin, et al., 2016). The process begins with the retention and modification of low-density lipoprotein (LDL) particles, specifically oxidized LDL (ox-LDL), which triggers an immunological response. When macrophages consume oxLDL through scavenger receptors, they produce foam cells that release reactive oxygen species (ROS) and pro-inflammatory cytokines. As CAD and atherosclerosis progress, these inflammatory mediators exacerbate plaque formation, smooth muscle cell proliferation, and endothelial dysfunction. In the end, unstable plaques that are prone to rupture develop, which is a significant cause of acute coronary events, including myocardial infarction. Inflammation and oxidative stress are the main causes of atherosclerosis progression.

ROS produced in endothelial and smooth muscle cells by NADPH oxidases (NOX2 and NOX4) reduces the bioavailability of nitric oxide (NO), resulting in oxidative stress and endothelial dysfunction (Förstermann et al., 2017). Plaque development is aided by vascular tone, platelet aggregation, and permeability to lipoproteins all increasing when endothelial function is subsequently reduced (Keaney, 2000). Moreover, ROS-induced lipid peroxidation generates toxic aldehydes such as 4-hydroxynonenal (4-HNE), which change cellular lipids and proteins and trigger further inflammatory reactions (Ayala et al., 2014). Endothelial dysfunction results from the uncoupling of endothelial nitric oxide synthase (eNOS), which alters its activity from producing NO to superoxide anions ( $O_2^-$ ), intensifying oxidative damage (Janaszak-Jasiecka et al., 2023). Additionally, lipoprotein-associated phospholipase A2 (Lp-PLA2) promotes inflammation and plaque development by hydrolyzing oxidized phospholipids on LDL particles (Pantazi et al., 2022). These pathophysiological processes impair coronary blood flow and reduce oxygen delivery to myocardial tissue, leading to ischemia. Persistent ischemia and repeated plaque rupture

events ultimately compromise cardiac function, weaken myocardial contractility, and may lead to heart failure, arrhythmias, or sudden cardiac death. Thus, the heart bears the primary burden of these atherosclerotic changes through direct structural and functional damage.

### **Systemic Vasculitis and Its Impact on Atherosclerosis**

Systemic vasculitis, a condition marked by inflammation of the blood vessels, is a significant contributor to the pathogenesis of atherosclerosis (Guillevin & Dörner, 2007). Vascular wall damage is the outcome of vasculitis-induced immune system activation. In conditions like giant cell arteritis (GCA), dendritic cells stimulate T-cells, attracting neutrophils and macrophages that harm the endothelium. Complement pathways are triggered by immune complexes that are deposited in the artery walls in various vasculitic diseases, such as polyarteritis nodosa and cryoglobulinemia, and this exacerbates the inflammatory response (Chimenti et al., 2015). This chronic inflammatory environment accelerates the development of atherosclerotic plaques by attracting immune cells that generate pro-inflammatory cytokines and matrix metalloproteinases (MMPs), which degrade the extracellular matrix and destabilize plaques (Song et al., 2022). Vasculitis also increases the risk of plaque development and exacerbates endothelial dysfunction by producing endothelin-1 (ET-1), a potent vasoconstrictor (Konukoglu & Uzun, 2017). To raise the risk of cardiovascular events like myocardial infarction and stroke, atherosclerosis and vasculitis combine.

### **Epigenetic and genetic variables have a major role in the development of CAD and atherosclerosis.**

Through genome-wide association studies (GWAS), several significant genetic loci associated with endothelial function, inflammation, lipid metabolism, and vascular smooth muscle cell activity have been identified (Erbilgin et al., 2015). Notable genes include MIA3, which is involved in collagen production and smooth muscle cell proliferation, and SIRT1, which induces endothelial nitric oxide synthase (eNOS) expression to avoid endothelial dysfunction (Fräk et al., 2022). Plaque stability is influenced by TCF21, a regulator of smooth muscle cell phenotype, whereas LDLR and APOA5 have an impact on lipid deposition in arteries, with mutations raising the risk of CAD (Butnariu et al., 2022). Genes related to inflammation and lipid metabolism are also influenced by epigenetic regulation, specifically DNA methylation. Gene expressions are regulated by DNA methyltransferases (DNMTs) and TET proteins (Jung & Kang, 2021). In mouse models, atherosclerotic lesions have been demonstrated to decrease when epigenetic pathways

are altered, such as by overexpressing TET2 (Liu et al., 2018). Potential therapeutic approaches for the prevention or treatment of CAD involve focusing on these genetic and epigenetic pathways (Schiano et al., 2020). Furthermore, therapeutic strategies aimed at reducing oxidative stress and inflammation are being investigated. For instance, SGLT-2 inhibitors may lessen inflammation and oxidative stress in CAD patients, while the antioxidant compound SG-1002 has demonstrated promise in lowering the burden of atherosclerotic plaque (Roth et al., 2023). Concentrating on Gasdermin D, a protein implicated in plaque stability, is another treatment option to prevent plaque rupture and reduce acute coronary events. Furthermore, by modifying microRNAs (miRNAs), including miR-21, implicated in inflammation and smooth muscle cell proliferation, plaques may be stabilized and their rupture prevented (Rampin et al., 2024).

The pathophysiology of cardiovascular diseases (CVDs), which are nevertheless a major global health problem, is significantly regulated by pathologic microRNAs (miRNAs) (Çakmak & Demir, 2020). These small, non-coding RNAs affect several processes that contribute to the development of CVD and change the expression of genes. Several cardiovascular disorders have been associated with particular miRNAs, such as miR-133a, miR-21, miR-499a-5p, miR-1, and miR-126. TAGLN2 and FSCN1, two genes involved in smooth muscle growth and cardiac contractility, are targeted by miR-133a, which regulates atherosclerosis and cardiac hyperplasia (Sessa et al., 2023). Elevated miR-21 is linked to heart failure and myocardial infarction (MI). It targets PDCD4, RASGRP1, and BTG2, altering apoptosis and stress responses to encourage fibrosis (Badimon et al., 2021). Cardiotoxicity is avoided by miR-499a-5p by altering genes associated with cardiomyocyte survival, particularly after ischemic stress or chemotherapy (Fa et al., 2021). Other miRNAs, such as miR-1 and miR-126, regulate genes essential for maintaining the integrity of endothelial cells and cardiac muscle function, respectively, to influence the structure, function, and inflammation of the heart (Henning, 2021).

### **Bioinformatics Tools for miRNA Research in CVDs**

Recent developments in bioinformatics have significantly enhanced the personalized investigation of miRNAs in cardiovascular diseases (CVDs) (Kunz et al., 2015). Databases such as miRBase, miRTarBase, and TAM 2.0 play a critical role in identifying disease-specific miRNA-gene interactions and understanding their contribution to individual patient profiles (Singh et al., 2015). miRBase provides curated miRNA sequences that can be used to trace genetic variations related to cardiovascular pathology,

while miRTarBase offers experimentally validated target interactions relevant to heart disease. For instance, miR-133a-3p, which targets FSCN1 and TAGLN2—genes involved in smooth and cardiac muscle function—has been linked to disease-specific cardiac remodeling (Sessa et al., 2023). TAM 2.0 supports personalized analysis by mapping miRNAs to functional pathways and disease-specific gene expression patterns, especially in processes like myocardial apoptosis and cardiogenesis (Lu et al., 2010). These tools collectively enable the identification of individualized miRNA signatures, facilitating the development of targeted diagnostics and personalized therapeutic strategies in CVD care.

### **Therapeutic Implications and Challenges in Personalized miRNA-Based Treatments for CVDs**

miRNAs are emerging as key therapeutic agents in personalized cardiovascular care due to their ability to modulate disease pathways and improve heart function (Zhou et al., 2018). Personalized miRNA therapies aim to tailor interventions based on a patient's unique miRNA expression profile, allowing for precise targeting of disease mechanisms while minimizing off-target effects. However, challenges remain with delivery methods, stability, and potential immune responses. Advances such as lipid nanoparticles, exosomes, and viral vectors are being optimized for effective and patient-specific delivery (Dasgupta & Chatterjee, 2021). Personalized miRNA profiling supports the design of therapies that enhance efficacy and reduce adverse effects by aligning treatment with individual molecular signatures. Novel approaches, including therapeutic angiogenesis, gene therapy, and nanotechnology, are also being explored to promote tissue repair and vascular regeneration in a personalized manner (Nour et al., 2020). This shift toward individualized miRNA-based interventions marks a transformative step in the identification, prevention, and treatment of CVD.

### **Emerging Trends and Risk Factors in Cardiovascular Disease**

Cardiovascular illnesses are increasingly affecting younger individuals; rates of acute myocardial infarction (MI), ischemic stroke, and other CVDs are rising among people under 55, particularly among women (Chandrasekhar et al., 2018). Increases in obesity, type 2 diabetes, and lifestyle choices—including the use of e-cigarettes (electronic nicotine delivery systems)—have all contributed to the rise in young adults' risk of CVD (Górna et al., 2020). This population also experiences sleep deprivation, mental health issues, and socioeconomic variables, all of which are linked to poor cardiovascular health outcomes (Ubben et

al., 2024). Significant racial and ethnic differences are evident in the higher incidence of cardiovascular disease mortality, diabetes, and hypertension among Black and Hispanic populations (Kurian et al., 2007). To address the rising prevalence of CVDs in young adults, prevention and intervention strategies—such as tailored healthcare, policy modifications, and community-based programs—are essential. Early identification and management of risk factors, along with education and lifestyle modifications, are essential to reducing the future burden of cardiovascular diseases in this demographic (Joseph et al., 2017).

Despite a general decrease in mortality, recent trends show a worrying increase in cardiovascular disease (CVD) among young adults (Andersson & Vasan, 2018). Over the past 20 years, the prevalence of acute myocardial infarctions (MIs) in people under 55 has risen from 27% to 32%, and young women, especially those between the ages of 35 and 44, have seen a significant increase in mortality from CVD (Gulati et al., 2020). Hospitalizations for acute ischemic stroke in people aged 18 to 44 have more than doubled, particularly among men in this age range (Tibæk et al., 2016). This pattern is a reflection of the increasing prevalence of both established risk factors like obesity, type 2 diabetes, and hypertension, as well as newer ones like e-cigarette use and poor sleep quality. Black and Hispanic populations have more severe and earlier-onset forms of cardiovascular disease (CVD), which are made worse by socioeconomic factors, healthcare access, and psychological stressors. Racial and ethnic disparities are especially noticeable in these populations.

### **Factors Associated with Young Adult Cardiovascular Risk**

Young adulthood is a critical period during which long-term cardiovascular health is shaped by behavioral, psychosocial, and environmental factors. Marked declines in cardiovascular health (CVH) metrics—such as physical activity, diet quality, and body mass index (BMI)—highlight poor adherence to heart-healthy behaviors in this demographic (Park et al., 2020). In particular, chronic sleep deprivation, now affecting a significant portion of young adults, contributes to metabolic disturbances including insulin resistance and elevated blood pressure (Miller & Cappuccio, 2007).

Psychosocial stressors such as depression, anxiety, and adverse childhood experiences (ACEs) play a significant role in the development and progression of cardiovascular disease (CVD), often influencing lifestyle choices like smoking, overeating, and inactivity (Carola et al., 2024).

These factors are often compounded by limited access to mental health and preventive services.

Environmental and neighborhood conditions further influence cardiovascular risk. Limited access to healthy food, safe recreational spaces, and healthcare—common in low-income communities—can predispose young adults to obesity and metabolic dysfunction (Candib, 2007). High-stress environments, including neighborhoods with low social cohesion or high crime rates, exacerbate these risks. Early signs of vascular dysfunction, such as arterial stiffness and endothelial damage, have been observed in adolescents and may be accelerated by ongoing environmental exposures (Steinberger et al., 2009).

Prevention strategies in this age group should include both primordial (societal-level) and primary (individual-level) approaches. Primordial prevention efforts—such as policies promoting urban planning for active living, taxing unhealthy foods, or regulating tobacco marketing—are vital to reducing population-wide risk factors (Weintraub et al., 2011). Meanwhile, primary prevention should offer tailored interventions like dietary counseling, physical activity programs, and early pharmacological treatment for young individuals with elevated cardiovascular risk. Technology-enabled solutions such as telemedicine and mobile health applications can improve access, especially for time-constrained young adults (Turvey & Fortney, 2017). By addressing both individual behaviors and structural determinants, a comprehensive prevention strategy can reduce the future burden of CVD in this population.

### **Research Opportunities and Directions in Cardiovascular Health Among Young Adults**

Given the rising incidence of cardiovascular disease (CVD) in young adults, targeted research is necessary to address the unique risk factors that this demographic faces. This study focuses specifically on young adults because recent epidemiological trends indicate a concerning increase in early-onset CVD in individuals under 55, particularly among women. While older adults remain the most affected group in terms of mortality, early intervention in younger populations presents a critical window to prevent lifelong disease progression and reduce long-term healthcare burdens. Therefore, this study intentionally excluded elderly populations to prioritize a growing but under-addressed at-risk group. Primordial prevention should focus on lowering risk factors that impact the entire population. Future generations' cardiovascular habits will be greatly impacted by public health programs that encourage physical activity, healthy eating, and reduced tobacco use. Clinical trials are necessary to find effective interventions for young adults, particularly those with behavioral, psychosocial, or genetic risk factors. High-risk groups are given priority in

intervention studies, such as individuals with multiple risk behaviors, women with high-risk pregnancies, and those who have experienced adverse childhood experiences (ACEs). Implementation science research can also help evaluate strategies for effectively integrating preventative care in real-world settings using digital tools like mobile health applications and electronic health records, which can increase young adults' involvement and adherence.

Socioeconomic status (SES) has a significant impact on biological risk factors and access to healthcare, making it a significant determinant in cardiovascular health (Schultz et al., 2018). Among teens from lower socioeconomic backgrounds, smoking, poor diet, and inactivity are risk factors for cardiovascular disease (CVD) in later life. Furthermore, childhood SES has a persistent effect on cardiovascular outcomes into adulthood, even after controlling for adult SES. This issue is further complicated by racial and ethnic disparities, particularly for Black and Hispanic populations, who are more susceptible to CVD due to a confluence of genetic predispositions, environmental stressors, and low socioeconomic status. Systemic inequities such as differences in access to healthcare and social assistance exacerbate these discrepancies. Therefore, addressing racial disparities in cardiovascular health and SES should be the main focus of future research and intervention efforts.

### **Mechanisms of Cardiovascular Disease in Young Adults and Preventive Strategies**

Atherosclerosis starts in childhood and advances through adolescence and the early stages of adulthood. Because atherosclerotic lesions can be found in late adolescence, early intervention is essential. This means that preventive measures should be put in place before overt disease manifests. Atherosclerotic plaque development is accelerated by factors like smoking, obesity, hypertension, and high cholesterol, which also encourage endothelial dysfunction, oxidative stress, and inflammation (Rafieian-Kopaei et al., 2014). Plaque accumulation results from oxidative stress, which is brought on by smoking, poor eating habits, and inactivity. Familial hypercholesterolemia, a genetic factor, can exacerbate the effects of lifestyle factors on cardiovascular health. Early detection and treatment of type 2 diabetes and hypertension are critical because they significantly predict future cardiovascular events (Herder et al., 2011).

Although elderly individuals bear the highest burden of cardiovascular disease in terms of prevalence and mortality, this study focuses on young adults to address the growing trend of early-onset CVD. Intervening earlier in the disease continuum provides an opportunity to reduce the lifetime

risk of cardiovascular complications and ultimately lower the disease burden in older age. Recognizing the vulnerability of elderly populations remains essential for clinical care, while this review emphasizes prevention strategies aimed at delaying disease onset from an earlier age.

Prevention strategies should be centered on primary prevention (interventions directed at high-risk individuals) and primordial prevention (interventions at the population level). While new digital health technologies, such as wearables and mobile health apps, offer promising tools for ongoing monitoring and behavioral change, healthcare systems must strengthen engagement by addressing barriers like insurance access and care gaps (Smuck et al., 2021).

### **Risk Factors and Biomarkers in Pediatric Cardiovascular Disease**

Conventional and non-conventional risk factors both affect children's cardiovascular disease (CVD). Conventional risk factors that contribute to early-onset CVD include family history, age, sex, obesity, hypertension, dyslipidemia, and diabetes. These risk factors are becoming more common in children. Poor diet, inactivity, and tobacco use are examples of behavioral and lifestyle factors that increase these risks. The two physiological factors that are especially concerning as modifiable are hypertension and dyslipidemia. The development of metabolic syndrome and atherosclerosis is largely influenced by obesity and insulin resistance (Grundy, 2002).

While many risk factors and biomarkers overlap between pediatric and adult populations, children often present with earlier manifestations and developmental influences, and some biomarkers may have different predictive values or emerging significance in pediatric CVD. Therefore, non-traditional biomarkers are being explored to improve early risk assessment and intervention specifically in pediatric populations, as their pathophysiology and progression may differ from adults. The onset of atherosclerosis cannot be fully explained by these factors, which calls for more research into nontraditional biomarkers to improve early risk assessment and intervention in pediatric populations.

### **Biomarkers for Early Cardiovascular Risk in Youth**

Biomarkers are essential resources for comprehending the course of a disease, forecasting outcomes, and directing interventions related to cardiovascular health in children (Balagopal et al., 2011). In addition to being modifiable by treatment, ideal biomarkers should be reproducible, biologically plausible, and economical. Finding trustworthy biomarkers for the early prediction of CVD is still a top priority despite known risk factors, especially as childhood

obesity and metabolic disorders increase. Because CVD events occur quite late in life, it is difficult to establish direct correlations between biomarkers and hard cardiovascular outcomes like myocardial infarction (MI) in young people. On the other hand, surrogate markers, such as carotid intima-media thickness (IMT), provide valuable insights into subclinical atherosclerosis and the long-term effects of risk factors present from age one (Willeit et al., 2011).

Key biomarkers associated with early cardiovascular risk factors in youth include elevated levels of high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) reflecting inflammation, fasting insulin and hemoglobin A1c indicating insulin resistance and glycemic control, lipid profiles such as LDL-C and triglycerides indicating dyslipidemia, and blood pressure measurements as a biomarker of hypertension. Additionally, biomarkers of oxidative stress and endothelial dysfunction, like asymmetric dimethylarginine (ADMA) and oxidized LDL, are gaining attention for their roles in early vascular damage. Biomarkers that track an individual from childhood into adulthood may make it possible to detect and treat cardiovascular events early to prevent them in the future.

### **Adipocyte Dysfunction and Its Role in Cardiovascular Risk**

Adipocyte dysfunction plays a key role in the development of CVD, especially in childhood obesity. Overloaded adipocytes experience hypertrophy and hyperplasia, which disrupts normal fat metabolism and causes systemic inflammation (Lim et al., 2021). The accumulation of misfolded proteins in adipocytes leads to endoplasmic reticulum (ER) stress, which exacerbates inflammation and insulin resistance (Khan, & Wang, 2014). Dysfunctional adipocytes cause endothelial cell damage, promote atherosclerosis, and increase the risk of metabolic disorders by releasing proinflammatory cytokines like TNF- $\alpha$  and IL-6 (Engin, 2024). Because it causes dyslipidemia, insulin resistance, and endothelial dysfunction, the accumulation of free fatty acids (FFA) in non-adipose tissues also accelerates the formation of atherosclerotic plaques (Gumpen & Gumpen, 2019). The bioactive chemicals called adipokines, released by adipose tissue, are essential for controlling inflammation, insulin sensitivity, and vascular health. Increased leptin levels are associated with inflammation and endothelial dysfunction, while decreased adiponectin levels are linked to insulin resistance and poor vascular health (Prieto et al., 2014). Dysregulated secretion of adipokines, such as leptin and adiponectin, increases the risk of cardiovascular disease (Landecho et al., 2019).

## **Emerging Biomarkers and Mechanisms of Thrombosis in Cardiovascular Disease**

Novel markers of insulin resistance, oxidative stress, and inflammation are becoming recognized as significant risk factors for CVD in children. Children with obesity, metabolic syndrome, and early-stage atherosclerosis have higher levels of the markers of systemic inflammation and oxidative stress, including oxidized low-density lipoprotein (ox-LDL), C-reactive protein (CRP), and interleukin-6 (IL-6) (Petek & Varda, 2024). Because of their links to endothelial dysfunction and insulin resistance, CRP and IL-6 may be early markers of cardiovascular risk (Fernández-Real et al., 2003). Elevated oxLDL levels are a sign of oxidative stress and the onset of atherosclerotic plaque formation. Additionally important in CVD are hemostasis and thrombosis; in obese children, fibrinogen, platelet aggregation, and plasminogen activator inhibitor-1 (PAI-1) all contribute to a prothrombotic state (Altalhi et al., 2021). Plaque formation and clotting are encouraged by elevated fibrinogen, and thrombosis risk is further increased by PAI-1's inhibition of fibrinolysis. Elevated levels of D-dimer, a fibrin degradation product, indicate a heightened prothrombotic state and ongoing clot formation and degradation (Verni et al., 2020). Exercise is crucial for reducing cardiovascular risk, especially in obese children, as it has been demonstrated to decrease thrombosis biomarkers like fibrinogen, PAI-1, and D-dimer.

## **Machine Learning in Cardiovascular Disease Prevention: Innovations and Challenges**

Blood pressure (BP), particularly hypertension, is a major and primary risk factor for cardiovascular diseases (CVDs), including ischemic heart disease, stroke, heart failure, and kidney disease. BP is usually measured with intermittent cuffs. Given the complex interplay of multiple risk factors in CVD, the application of machine learning techniques to analyze diverse biomarkers—not limited to blood pressure—holds promise for simultaneously assessing and predicting cardiovascular risk more accurately. However, these conventional techniques cannot record blood pressure fluctuations over time, particularly when engaging in various activities or under stress. At-home or continuous blood pressure monitoring is crucial to overcoming this constraint. Pulse transit time (PTT) and pulse wave analysis (PWA) are two methods used by emerging technologies, like cuffless blood pressure measurement tools, to estimate blood pressure non-invasively. Despite encouraging outcomes, these devices' widespread clinical use is hampered by issues with accuracy, calibration, and external validation. There was no discernible difference between smartphone-enhanced blood pressure cuffs and conventional ones in a randomized trial, highlighting the

necessity of additional technological validation before adoption (Watson et al., 2019).

## **Role of Sleep and Diabetes in Cardiovascular Disease Risk**

Reports have shown that both short sleep durations (less than five hours) and lengthy sleep durations (greater than nine hours) are linked with an increased risk of cardiovascular disease (CVD) (Buxton et al., 2010; Ubhenin et al., 2024). Cardiovascular disease (CVD) risk is also raised by Sleep disorders including sleep apnea exacerbates heart failure, cardiovascular disease, and hypertension (Ubhenin et al., 2024). Wearable technology, such as fitness trackers and smartwatches, uses sensors like photoplethysmography (PPG) and accelerometers to monitor the quality of sleep; however, PSG is more accurate by comparison (de Zambotti et al., 2024). To detect sleep abnormalities, Google Nest Hub and other contactless sleep-tracking devices employ radar and microphones (Hamza, 2023). Conditions such as obstructive sleep apnea (OSA) are then detected using machine learning (ML) algorithms that have been trained on PSG data (Sheta et al., 2021). By resulting in arterial damage, increased inflammation, and endothelial dysfunction, diabetes, especially type 2, also contributes significantly to CVD. Wearable sensors, machine learning (ML) models, and continuous glucose monitoring (CGM) devices not only enable real-time tracking of glucose changes but also help customize diabetes management by predicting blood glucose trends based on activity, stress, and dietary inputs (Lu et al., 2023).

## **Machine Learning in Poly-Omic Risk Assessment for Cardiovascular Disease**

Poly-omic risk assessments incorporate data from clinical, environmental, genetic, and epigenetic sources to enhance cardiovascular risk prediction (Wheeler et al., 2014). Machine learning has revolutionized this field by integrating a variety of data types into trustworthy predictive models. Polygenic risk scores (PRS), which incorporate multiple genetic variations associated with coronary artery disease (CAD), have been shown to outperform traditional risk scores such as the Framingham Risk Score (Klarin & Natarajan, 2022). Machine learning models that analyze genetic and epigenetic data, such as patterns of DNA methylation and histone modification, can provide a deeper understanding of the causes of disease. For example, random forest models using genetic and epigenetic information have improved the sensitivity (0.70) for coronary heart disease prediction (Philibert et al., 2023). Additionally, ML can assist in identifying CAD molecular

subtypes, allowing for more individualized preventative measures (DeGroat et al., 2024).

### **Clinical and Ethical Challenges in Applying Machine Learning to Cardiovascular Disease Prevention**

The fragmented healthcare data is one of the main obstacles to the clinical integration of machine learning for the prevention of cardiovascular disease. Data sharing is restricted by privacy laws like HIPAA, which makes it more difficult to create large-scale machine-learning models (White et al., 2022). For machine learning to work well, it requires high-quality, diverse, and reproducible datasets (Prior et al., 2020). The lack of diversity in healthcare datasets may limit the generalizability of machine learning algorithms. Standardization of wearable data is necessary to provide cross-platform interoperability. Furthermore, there are concerns about the interpretability of ML models because of their "black-box" character, which is regularly criticized. Improving ML algorithms' transparency—for example, by showing model features—and educating doctors on how to incorporate ML predictions into patient-centered care are necessary to build trust in these technologies (Ahmed et al., 2020). Furthermore, to guarantee that ML models are impartial and equitable in their predictions, it is imperative to address the fairness of digital health instruments, particularly in populations with a range of skin tones (Rajkumar et al., 2018).

### **Nontraditional Risk Factors in Pediatric Cardiovascular Disease (CVD)**

Children's cardiovascular disease (CVD) is influenced by excess adiposity, especially visceral fat, through several cellular processes (Herouvi et al., 2013). When the capacity of adipocytes to store fat is exceeded, overnutrition results in adipocyte hypertrophy (enlargement) and hyperplasia (increased number) (Haczeyni et al., 2018). This malfunction results in endoplasmic reticulum (ER) stress, which disrupts cellular functions and causes insulin resistance and systemic inflammation (Hummasti & Hotamisligil, 2010). Furthermore, an accumulation of excess fat causes lipotoxicity and produces toxic chemicals by adipocytes that exacerbate inflammation and insulin resistance (Ahmed et al., 2021). These cellular abnormalities lead to metabolic dysfunction, specifically elevated triglycerides, and are significant contributors to childhood CVD (Aggoun et al., 2007).

Adipose tissue functions as an endocrine organ that regulates cardiovascular and metabolic health through the secretion of adipokines like leptin, adiponectin, and resistin (Ronti et al., 2006). Leptin resistance, which affects appetite regulation and energy expenditure and is a

consequence of obesity, is linked to an increased risk of cardiovascular disease (Pan et al., 2014). Reduced adiponectin levels in obese children are associated with insulin resistance and a higher risk of cardiovascular disease (Frithioff-Bøjsøe et al., 2020).

### **Oxidative Stress and Mitochondrial Dysfunction in Pediatric CVD**

An excess of reactive oxygen species (ROS), harms DNA and mitochondrial structures, leading to mitochondrial dysfunction brought on by obesity and overeating (Nevoit et al., 2024). Increased cardiovascular risk and insulin resistance are closely associated with this disorder. Furthermore, too much ROS synthesis causes oxidative stress, an imbalance between ROS and antioxidants that damages cell and starts inflammatory processes. Ultimately, this oxidative damage promotes atherosclerosis by producing important risk factors for CVD, such as insulin resistance, hyperglycemia, dyslipidemia, and vascular damage (Beverly & Budoff, 2020). Biomarkers of oxidative stress, such as F2-isoprostanes and malondialdehyde (products of lipid peroxidation), have been demonstrated to correlate with conventional risk factors for cardiovascular disease in children and could be used as early monitors of cardiovascular damage (Davies & Roberts, 2011).

### **Inflammatory Markers and Endothelial Dysfunction as CVD Biomarkers**

The development of atherosclerosis is significantly influenced by inflammation, and several inflammatory markers are linked to an increased risk of CVD in children. Atherosclerosis is preceded by vascular inflammation and endothelial dysfunction, which are facilitated by cytokines like TNF- $\alpha$  and IL-6, which are increased in insulin resistance and obesity (Henning, 2021). Retinol binding protein 4 (RBP4) is another adipokine that may be a biomarker for the risk of cardiovascular disease in children because it has been connected to childhood obesity and insulin resistance (Ji et al., 2022). Von Willebrand factor (vWF) and e-selectin are two markers of endothelial dysfunction that have been shown to predict cardiovascular risk in adults (Constans & Conri, 2006). New research indicates that these markers may also be early indicators of cardiovascular risk in children, especially those who are obese. Thrombosis-related biomarkers, which include tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1), are associated with the control of clot formation (Tsantarliotou et al., 2019). The prothrombotic state brought on by high levels of PAI-1 in obesity raises the risk of clot formation and subsequent cardiovascular events (Ciavarella et al., 2021).

### **Insulin Resistance and Its Role in Pediatric CVD**

Insulin resistance is a key cause of cardiovascular disease in children and is facilitated by oxidative stress, chronic inflammation, adipocyte dysfunction, and disruption of glucose metabolism (Petek et al., 2024). In insulin resistance, the accumulation of visceral fat leads to endoplasmic reticulum (ER) stress, mitochondrial malfunction, and lipotoxicity (Ahmed et al., 2021). These processes trigger systemic inflammation and metabolic imbalance, which promote endothelial dysfunction, activation of clotting pathways, and the development of atherosclerosis. Hyperinsulinemia, another consequence of insulin resistance, accelerates atherosclerosis by activating signaling pathways that stimulate vascular smooth muscle cell proliferation and clotting factor production (Bansilal et al., 2007).

In addition to insulin resistance, other metabolic conditions such as diabetes, hypertension, dyslipidemia, and obesity play crucial roles in pediatric CVD development and its complications (Nweze et al., 2017). Diabetes exacerbates vascular damage through chronic hyperglycemia-induced oxidative stress and inflammation, impairing endothelial function and accelerating atherosclerotic plaque formation. Hypertension contributes to vascular injury and cardiac remodeling by increasing arterial stiffness and promoting inflammation. Dyslipidemia, characterized by elevated LDL cholesterol and triglycerides and low HDL cholesterol, leads to lipid accumulation within arterial walls, further driving atherosclerosis. Obesity, particularly central adiposity, amplifies these risks by promoting insulin resistance, systemic inflammation, and adverse metabolic profiles. Together, these interrelated metabolic abnormalities create a complex network that heightens cardiovascular risk from childhood.

### **Inflammation and Thrombosis in Obesity-Related Cardiovascular Disease (CVD) Risk in Children.**

The pathophysiology of both atherosclerosis and thrombosis is significantly influenced by inflammation, with cytokines like TNF- $\alpha$ , interleukin-6, and C-reactive protein (CRP) promoting a prothrombotic state (Oikonomou et al., 2020). These cytokines increase the risk of thrombosis by promoting platelet aggregation, inducing fibrinogen production, and activating plasminogen activator inhibitor-1 (PAI-1) (Cesar et al., 2010). Obesity, particularly visceral adiposity, causes adipocytes to release inflammatory cytokines, which initiate a series of inflammatory reactions that worsen thrombotic tendencies. This inflammatory milieu increases the risk of cardiovascular disease (CVD), which is exacerbated in

children who are obese due to elevated levels of fibrinogen, PAI-1, and D-dimer (Welsh, 2008). Due to their indication of an early prothrombotic state, these biomarkers raise concerns about the long-term cardiovascular health of obese children. Early lifestyle changes, like eating healthier and exercising more, can improve these biomarkers and reduce the chance of developing CVD onward. Further longitudinal research is required to ascertain the long-term effects of these elevated biomarkers and validate their predictive importance for CVD in pediatric populations.

### **Future Directions in CVD Management and Monitoring in Pediatric Populations**

Cardiovascular disease (CVD), while traditionally considered an adult condition, is increasingly recognized as a significant health concern in pediatric populations. Studies estimate that early markers of CVD, including subclinical atherosclerosis and endothelial dysfunction, are present in approximately 5-10% of children with risk factors such as obesity, diabetes, or familial hypercholesterolemia (Hong, 2010). This prevalence underscores the urgent need for early identification and intervention to prevent progression into adult cardiovascular disease. Future studies on biomarkers including C-reactive protein (CRP), intercellular adhesion molecule-1 (ICAM-1), and plasminogen activator inhibitor-1 (PAI-1) must focus on clarifying their predictive value in children's cardiovascular risk stratification. Longitudinal investigations are crucial to elucidate the long-term implications of elevated thrombosis indicators in pediatric cohorts. The potential of these biomarkers to forecast cardiovascular events in children is particularly promising. A key emerging area involves integrating biomarker data with advanced digital health technologies. Machine learning (ML) models offer the capability to synthesize biomarker profiles, imaging data, and wearable device metrics (such as heart rate variability and physical activity) to provide real-time cardiovascular risk assessments tailored to pediatric patients (Javaid et al., 2022). This convergence of multi-modal data enables more precise and dynamic monitoring than traditional approaches. Personalized medicine approaches leveraging multi-omic data—including genomic, clinical, and lifestyle factors—will be pivotal in identifying at-risk children and tailoring preventive or therapeutic interventions (Mohammadi-Shemirani et al., 2023). For instance, ML-enhanced models for glucose management and continuous glucose monitoring (CGM) are promising, although clinical validation remains a barrier for many consumer sleep trackers (CSTs), which lack FDA certification due to concerns about accuracy and regulation.

Looking ahead, novel therapies such as regenerative medicine, microRNA-based drugs, and customized treatment strategies targeting molecular mechanisms of CVD could transform pediatric cardiovascular care (Alradwan et al., 2024). These advancements promise improved patient outcomes by delivering more specialized and effective treatments, ultimately enhancing the quality of life.

## Conclusion

Cardiovascular disease (CVD) pathogenesis involves a complex interplay of inflammation, hemostasis, oxidative stress, insulin resistance, and adipocyte dysfunction (Ubhenin et al., 2016; Donia & Khamis, 2021). Recent advances in biomarker research and digital health technologies offer promising avenues to revolutionize the early detection and management of CVD, particularly in pediatric and high-risk populations (Ullah et al., 2023). To effectively reduce the global burden of CVD, several key actions must be prioritized.

Firstly, there is an urgent need to validate and integrate biomarkers such as C-reactive protein (CRP), interleukins, adipokines, and thrombosis markers into routine clinical practice. These biomarkers have significant potential for early risk stratification and personalized monitoring, especially in children and young adults who may present with subclinical disease. Implementing these indicators in clinical workflows can enhance early intervention and improve outcomes.

Also, leveraging digital health technologies and machine learning models is essential for advancing personalized cardiovascular care. Wearable devices combined with ML-enhanced algorithms can provide real-time, individualized risk assessments, enabling timely and targeted interventions. However, standardized validation of these technologies and efforts to address disparities in accessibility are critical to ensure their broad and equitable impact.

Lifestyle and preventive interventions remain foundational to reducing cardiovascular risk. Evidence consistently supports that modifications such as dietary changes, increased physical activity, and weight management can lower prothrombotic and inflammatory markers. Integrating these strategies into public health policies and clinical guidelines is vital to promoting cardiovascular health across populations.

Furthermore, advancing research into molecular and mitochondrial targets presents new therapeutic possibilities. Therapies aimed at mitigating oxidative stress and improving mitochondrial function hold promise for innovative treatments that address the underlying

mechanisms of CVD. Continued investment in longitudinal studies and genetic profiling will be crucial to refine and personalize these approaches.

Finally, a multimodal, personalized approach that combines multi-omic biomarker data, digital health tools, and targeted therapeutics is needed to optimize prevention and treatment strategies. Such integrated efforts will enhance early detection and intervention, ultimately improving long-term cardiovascular outcomes.

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## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Declarations

### Ethics approval and consent to participate

All the studies involving experimental animals were carried out as specified in the ARRIVE guidelines National Institute of Health Guide for Laboratory Animal Care and Use (Pub No. 85-23, revised 1985) together with the ethical procedure of the Ethics and Biosafety Committee of the Faculty of Biological Sciences, University of Nigeria, Nigeria (ethical approval number: UNN/FBS/EC/1075).

*Loranthus micranthus* leaves were collected from different wild host trees, *Psidium guajava* and *Parkia biglobosa*, as stipulated in the University of Nigeria, Nsukka Institutional Guidelines for Plant Collection. A plant taxonomist, Mr. Alfred Ozioko, collected the plant. The farmers who owned the various plant fields gave permission to collect the plants.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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### Abbreviations

<i>Ab</i>	<i>Antibody</i>
<i>CP</i>	<i>Cyclophosphamide</i>
<i>DTH</i>	<i>Delayed-type hypersensitivity</i>
<i>DLC</i>	<i>Differential leukocyte counts</i>
<i>HA</i>	<i>Hemagglutination antibody</i>
<i>Ig</i>	<i>Immunoglobulin;</i>
<i>IFN</i>	<i>Interferon</i>
<i>IL-4</i>	<i>interleukins-4</i>
<i>JAK/STAT</i>	<i>Janus kinases -signal transducer and activator of transcription proteins</i>
<i>LD<sub>50</sub></i>	<i>Lethal Dose</i>
<i>L. micranthus</i>	<i>Loranthus micranthus</i>
<i>LMPBE</i>	<i>L. micranthus epiphytic on Parkia biglobosa</i>
<i>LMPGE</i>	<i>L. micranthus extracts epiphytic on Psidium guajava</i>
<i>MAPk</i>	<i>Mitogen-activated protein kinases</i>
<i>NF-κB</i>	<i>Nuclear factor-κB</i>
<i>SRBCs</i>	<i>Sheep red blood cells</i>
<i>TLC</i>	<i>Total leukocyte counts TNF-<math>\alpha</math>      tumour necrosis factor-<math>\alpha</math>.</i>

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<i>Ab</i>	<i>Antibody</i>	Andersson, C., & Vasan, R. S. (2018). Epidemiology of cardiovascular disease in young individuals. <i>Nature Reviews Cardiology</i> , 15(4), 230-240.
<i>CP</i>	<i>Cyclophosphamide</i>	
<i>DTH</i>	<i>Delayed-type hypersensitivity</i>	
<i>DLC</i>	<i>Differential leukocyte counts</i>	
<i>HA</i>	<i>Hemagglutination antibody</i>	
<i>Ig</i>	<i>Immunoglobulin</i>	
<i>IFN</i>	<i>Interferon</i>	Badimon, L., Robinson, E. L., Jusic, A., Carpusca, I., DeWindt, L. J., Emanueli, C., ... & Devaux, Y. (2021). Cardiovascular RNA markers and artificial intelligence may improve COVID-19 outcome: a position paper from the EU-Cardio RNA COST Action CA17129. <i>Cardiovascular Research</i> , 117(8), 1823-1840.
<i>IL-4</i>	<i>interleukins-4</i>	
<i>JAK/STAT</i>	<i>Janus kinases -signal transducer and activator of transcription proteins</i>	
<i>LD<sub>50</sub></i>	<i>Lethal Dose</i>	
<i>L. micranthus</i>	<i>Loranthus micranthus</i>	
<i>LMPBE</i>	<i>L. micranthus epiphytic on Parkia biglobosa</i>	
<i>LMPGE</i>	<i>L. micranthus extracts epiphytic on Psidium guajava</i>	
<i>MAPk</i>	<i>Mitogen-activated protein kinases</i>	Balagopal, P., De Ferranti, S. D., Cook, S., Daniels, S. R., Gidding, S. S., Hayman, L. L., ... & Steinberger, J. (2011). Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic, research, and clinical considerations for youth: a scientific statement from the American Heart Association. <i>Circulation</i> , 123(23), 2749-2769.
<i>NF-κB</i>	<i>Nuclear factor-κB</i>	
<i>SRBCs</i>	<i>Sheep red blood cells</i>	
<i>TLC</i>	<i>Total leukocyte counts TNF-α</i> <i>tumour necrosis factor-α</i> .	
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