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Immunometabolic Pathways in Cardiovascular Disease: Inflammation and Metabolic Dysfunction Beyond Traditional Risk Factors

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ABSTRACT

Cardiovascular disease remains the leading cause of mortality worldwide, despite significant advances in prevention and treatment strategies. Increasing evidence indicates that traditional risk factors alone are insufficient to fully explain cardiovascular risk, highlighting the importance of inflammatory and metabolic mechanisms in the development and progression of atherosclerotic disease. This review synthesizes current scientific evidence on the role of chronic low-grade

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inflammation and metabolic dysregulation as interconnected determinants of cardiovascular risk. The analysis integrates mechanistic, clinical, and population-level data describing how immune activation, insulin resistance, obesity, metabolic syndrome, and endothelial dysfunction interact to promote atherosclerosis and related cardiovascular outcomes. Particular attention is given to inflammatory signaling pathways, immune cell involvement, and the concept of residual inflammatory risk, which persists even in the presence of optimal lipid control. Additionally, the review examines the contribution of lifestyle factors as upstream modulators of immunometabolic processes. By adopting an integrative immunometabolic perspective, this review provides a comprehensive framework for understanding cardiovascular risk beyond conventional models. This approach is especially relevant for educational and clinical contexts in regions undergoing epidemiological transition, including Mexico, Colombia, and Ecuador. The findings support the incorporation of inflammatory and metabolic determinants into cardiovascular risk assessment, prevention strategies, and future research agendas.
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KEYWORDS

Cardiovascular risk, inflammation, metabolic syndrome, atherosclerosis, insulin resistance, residual inflammatory risk, immunometabolic mechanisms, endothelial dysfunction

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, representing a major public health challenge across both high-income and low- and middle-income countries. Despite significant advances in prevention, diagnosis, and treatment, the global burden of ischemic heart disease, stroke, and related cardiovascular conditions continues to rise, particularly in regions experiencing rapid epidemiological transition such as Latin America. In countries including Mexico, Colombia, and Ecuador, demographic aging, urbanization, and the growing prevalence of metabolic disorders have reshaped the cardiovascular risk profile, demanding renewed attention to underlying biological mechanisms that extend beyond traditional risk factors.

Historically, cardiovascular risk assessment has focused on dyslipidemia, hypertension, smoking, and diabetes mellitus as primary determinants of atherosclerotic disease. However, accumulating evidence over the past three decades has fundamentally transformed this paradigm by identifying chronic low-grade inflammation as a central driver of atherosclerosis and its clinical complications. Seminal work by Ross first proposed that atherosclerosis should be understood as an inflammatory disease of the arterial wall rather than a passive process of lipid accumulation [1]. This concept was subsequently expanded through experimental, clinical, and epidemiological studies demonstrating that inflammatory signaling pathways actively regulate plaque initiation, progression, and destabilization [2], [3].

At the molecular level, atherosclerosis is characterized by endothelial dysfunction, lipid retention within the intima, and the recruitment of immune cells—particularly monocytes and macrophages—that perpetuate a pro-inflammatory microenvironment. Cytokines, chemokines, and acute-phase reactants, including C-reactive protein (CRP), play a critical role in modulating vascular inflammation and have been consistently associated with adverse cardiovascular outcomes [4], [5]. These findings have reframed cardiovascular disease as a complex immunometabolic disorder, in which innate and adaptive immune responses interact closely with metabolic dysregulation.

Parallel to advances in vascular immunology, the global rise in obesity, insulin resistance, and metabolic syndrome has highlighted the importance of metabolic determinants in cardiovascular risk. Metabolic syndrome, defined by the clustering of central obesity, dyslipidemia, hypertension, and impaired glucose metabolism, has been robustly associated with increased cardiovascular morbidity and mortality [10]–[12]. Insulin resistance and hyperglycemia contribute directly to endothelial dysfunction, oxidative stress, and inflammatory activation within the vascular wall,

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thereby accelerating atherogenesis [7]. These mechanisms are particularly relevant in Latin American populations, where the prevalence of obesity and type 2 diabetes mellitus has increased markedly over recent decades.

Macrophages occupy a central position at the intersection of inflammation and metabolism in atherosclerosis. Beyond their role in lipid uptake and foam cell formation, macrophages exhibit remarkable phenotypic plasticity, adopting pro-inflammatory or resolving profiles depending on local metabolic and immunologic cues [8]. Dysregulated macrophage activation contributes not only to plaque growth but also to plaque instability, a key determinant of acute coronary syndromes. Moreover, emerging evidence suggests that autoimmune mechanisms and maladaptive immune responses further amplify vascular inflammation, underscoring the complexity of immune involvement in cardiovascular disease [9], [18].

Clinical and translational studies have reinforced the relevance of inflammation as a therapeutic target in cardiovascular prevention. Observational data linking elevated inflammatory biomarkers to cardiovascular events were complemented by interventional trials demonstrating that selective anti-inflammatory therapies can reduce cardiovascular risk independently of lipid lowering. The CANTOS trial provided compelling evidence that inhibition of interleukin-1β with canakinumab significantly reduced recurrent cardiovascular events, establishing inflammation as a modifiable component of residual cardiovascular risk [6], [19]. These findings have shifted attention toward a dual-target strategy in cardiovascular prevention, addressing both cholesterol burden and inflammatory activity [20].

In parallel, lifestyle-related factors—including diet, physical inactivity, and obesity—remain critical upstream drivers of both metabolic and inflammatory pathways. Large-scale studies have shown that unhealthy lifestyle patterns promote chronic systemic inflammation, thereby amplifying cardiovascular risk across diverse populations [14]. Obesity-induced hypertension, mediated through neurohormonal activation, vascular inflammation, and altered renal sodium handling, further exemplifies the tight coupling between metabolic dysfunction and cardiovascular pathology [13]. These interactions are especially pertinent in regions undergoing nutritional transition, where traditional dietary patterns are increasingly replaced by ultra-processed, calorie-dense foods.

Given this evolving understanding, contemporary cardiovascular research increasingly emphasizes the concept of "residual inflammatory risk," referring to the persistent risk of cardiovascular events despite optimal control of traditional risk factors [15], [19]. This concept is particularly relevant in clinical practice and public health strategies across Mexico, Colombia, and Ecuador, where resource constraints and heterogeneous healthcare systems necessitate integrated, mechanism-based approaches to risk stratification and prevention.

The present review aims to synthesize current evidence on the inflammatory and metabolic determinants of cardiovascular risk, integrating insights from vascular biology, immunology, and metabolic research. By examining key molecular mechanisms, clinical associations, and therapeutic implications, this work seeks to provide a comprehensive framework for understanding cardiovascular risk beyond conventional models. The central premise underlying this review is that inflammation and metabolic dysfunction are not merely coexisting phenomena but are mechanistically intertwined processes that jointly shape cardiovascular outcomes.

DEVELOPMENT

The contemporary understanding of cardiovascular risk has evolved from a unidimensional model centered on lipid accumulation to a multidimensional framework in which inflammatory and metabolic processes are recognized as central, interacting determinants of disease onset and progression. This shift reflects decades of experimental, clinical, and population-based research demonstrating that cardiovascular pathology emerges from the convergence of immune dysregulation, metabolic imbalance, and vascular dysfunction rather than from isolated risk factors alone.

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Inflammatory mechanisms in cardiovascular risk

Inflammation plays a fundamental role throughout all stages of atherosclerosis, from endothelial activation to plaque rupture and thrombosis. Early vascular injury triggers endothelial dysfunction, characterized by increased permeability to lipoproteins, upregulation of adhesion molecules, and recruitment of circulating immune cells. Low-density lipoproteins retained within the arterial intima undergo oxidative modification, promoting monocyte differentiation into macrophages and subsequent foam cell formation [1], [2]. These processes establish a self-sustaining inflammatory milieu that drives plaque expansion.

Macrophages represent a pivotal cellular component in this context. Beyond lipid uptake, they actively secrete pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α, which amplify local and systemic inflammation [8]. The phenotypic heterogeneity of macrophages further complicates plaque biology, as pro-inflammatory subsets contribute to plaque instability through matrix degradation and necrotic core expansion, increasing the risk of acute coronary events [3], [18].

Clinical evidence has consistently supported the relevance of inflammation as a determinant of cardiovascular risk. Elevated levels of inflammatory biomarkers, particularly C-reactive protein, have been shown to predict future cardiovascular events independently of traditional risk factors [5]. Importantly, this association persists even in individuals with well-controlled lipid profiles, highlighting inflammation as a distinct and clinically meaningful pathway [15], [19].

The causal role of inflammation has been further substantiated by means of targeted anti-inflammatory interventions. The demonstration that selective inhibition of IL-1β reduces recurrent cardiovascular events without altering lipid levels provided direct proof that inflammation is not merely a marker but an active driver of atherosclerotic disease [6]. These findings have reinforced the concept that residual inflammatory risk constitutes a major challenge in cardiovascular prevention strategies worldwide.

Metabolic determinants and their interaction with inflammation

Metabolic disorders exert profound effects on cardiovascular risk through both direct and indirect mechanisms. Insulin resistance and chronic hyperglycemia promote endothelial dysfunction, oxidative stress, and low-grade systemic inflammation, accelerating atherogenesis [7]. In this setting, metabolic abnormalities act synergistically with immune pathways, amplifying vascular injury.

The metabolic syndrome exemplifies this interaction, as it integrates central obesity, dyslipidemia, hypertension, and glucose intolerance into a unified risk phenotype strongly associated with cardiovascular morbidity and mortality [10]–[12]. Adipose tissue dysfunction in obesity contributes to this process by acting as an active endocrine organ that secretes pro-inflammatory adipokines while reducing anti-inflammatory mediators. This imbalance fosters chronic inflammation and alters lipid metabolism, thereby increasing atherosclerotic burden.

Hypertension associated with obesity further illustrates the inflammatory–metabolic nexus. Neurohormonal activation, renal sodium retention, and vascular remodeling are accompanied by inflammatory signaling that exacerbates arterial stiffness and endothelial dysfunction [13]. These mechanisms are particularly relevant in populations experiencing rapid increases in obesity prevalence, as observed in Mexico, Colombia, and Ecuador, where cardiovascular risk profiles increasingly reflect metabolic-driven pathophysiology.

High-density lipoprotein (HDL) cholesterol, traditionally viewed as cardioprotective, has also been re-evaluated within this framework. Beyond its role in reverse cholesterol transport, HDL exhibits anti-inflammatory and antioxidant properties that may be impaired in metabolic disease states [16]. Thus, qualitative alterations in lipoprotein function, rather than absolute lipid concentrations alone, contribute to cardiovascular risk in inflammatory and metabolic conditions.

Lifestyle factors as upstream drivers

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Lifestyle-related factors serve as critical upstream determinants of both inflammatory and metabolic dysregulation. Dietary patterns rich in saturated fats, refined carbohydrates, and ultra-processed foods promote obesity, insulin resistance, and systemic inflammation, whereas physical inactivity exacerbates these effects [14]. Conversely, lifestyle interventions targeting weight reduction, physical activity, and dietary quality have been shown to attenuate inflammatory biomarkers and improve metabolic profiles, underscoring their central role in cardiovascular prevention.

From a population perspective, these factors are especially relevant in regions undergoing epidemiological and nutritional transitions. The coexistence of traditional cardiovascular risk factors with emerging metabolic and inflammatory drivers necessitates integrated prevention strategies that address biological mechanisms alongside social and environmental determinants of health.

Integrated perspective on cardiovascular risk

Taken together, the evidence supports an integrated model in which inflammation and metabolism are deeply interconnected determinants of cardiovascular risk. Rather than acting independently, these processes form a dynamic network influencing vascular structure, immune responses, and clinical outcomes. The recognition of residual inflammatory risk has expanded therapeutic horizons beyond lipid lowering, emphasizing the need for comprehensive risk assessment and personalized prevention strategies [20].

For educational and clinical contexts, particularly within Latin America, this framework provides a biologically coherent basis for understanding cardiovascular disease as a systemic disorder. It also highlights the importance of aligning preventive and therapeutic approaches with the underlying immunometabolic mechanisms that shape cardiovascular risk across diverse populations.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To analyze and synthesize current scientific evidence on the inflammatory and metabolic determinants of cardiovascular risk, integrating molecular, clinical, and population-level perspectives in order to strengthen the understanding of cardiovascular disease as an immunometabolic process relevant to international contexts, including Mexico, Colombia, and Ecuador.

A. Cognitive Domain

1. To **identify** the principal inflammatory pathways involved in the initiation and progression of atherosclerosis, emphasizing their role in cardiovascular risk development [1]–[4].
2. To **explain** the metabolic mechanisms—such as insulin resistance, obesity, and metabolic syndrome—that contribute to cardiovascular disease through inflammatory and endothelial dysfunction processes [7], [10]–[13].
3. To **analyze** the interaction between immune responses and metabolic alterations in shaping residual cardiovascular risk beyond traditional lipid-based models [15], [19], [20].
4. To **evaluate** the clinical relevance of inflammatory biomarkers and anti-inflammatory therapeutic strategies in contemporary cardiovascular prevention [5], [6].

B. Psychomotor Domain

1. To **apply** theoretical knowledge of inflammatory and metabolic cardiovascular risk factors to the interpretation of clinical and epidemiological evidence presented in the literature.
2. To **organize** and **classify** cardiovascular risk determinants according to immunological and metabolic mechanisms for academic discussion and case-based learning.
3. To **integrate** scientific findings into structured analytical frameworks useful for academic presentations, critical reviews, and educational activities in cardiology and internal medicine.

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C. Affective Domain

1. To **recognize** the importance of inflammation and metabolic health remembering that cardiovascular disease extends beyond isolated risk factors and requires a systemic understanding.
2. To **value** the role of lifestyle modification and preventive strategies in reducing inflammatory and metabolic cardiovascular risk at both individual and population levels [14].
3. To **promote** critical thinking and ethical responsibility in the interpretation and application of cardiovascular research within diverse healthcare settings, particularly in Latin American contexts.

OBJECT OF STUDY

The object of study of this review is the complex interaction between inflammatory and metabolic processes as determinants of cardiovascular risk, understood as a multidimensional biological phenomenon that operates across molecular, cellular, systemic, and population levels. Rather than focusing on a single disease entity or a specific patient cohort, this work examines cardiovascular risk as an integrated pathophysiological system shaped by immune activation, metabolic dysregulation, and vascular dysfunction.

From a conceptual standpoint, the phenomenon under investigation is cardiovascular risk as an immunometabolic construct. This construct encompasses chronic low-grade inflammation, alterations in lipid and glucose metabolism, endothelial dysfunction, and immune system involvement in the initiation and progression of atherosclerotic disease. Atherosclerosis is therefore approached not merely as a consequence of lipid accumulation but as a dynamic inflammatory process modulated by metabolic conditions such as obesity, insulin resistance, metabolic syndrome, and hypertension [1], [3], [7].

At the biological level, the object of study includes the mechanisms through which inflammatory mediators—such as cytokines, acute-phase reactants, and immune cell signaling pathways—interact with metabolic disturbances to promote vascular injury. Particular attention is given to the role of macrophages, endothelial cells, adipose tissue–derived mediators, and lipoprotein functionality in shaping the inflammatory milieu that underlies cardiovascular pathology [8], [16], [18]. These mechanisms are examined as interconnected components of a single system rather than as isolated processes.

At the clinical level, the object of study extends to the determinants of residual cardiovascular risk, defined as the persistent risk of cardiovascular events despite optimal control of traditional factors such as low-density lipoprotein cholesterol. This includes the evaluation of inflammatory biomarkers, metabolic profiles, and their predictive value for cardiovascular outcomes, as well as the implications of anti-inflammatory and metabolic-targeted interventions in prevention strategies [5], [6], [19], [20]. The clinical dimension of the object of study is addressed indirectly, through the synthesis of published evidence, without reference to individual patients or identifiable populations.

From a population and public health perspective, this review considers cardiovascular risk within the context of global epidemiological transitions, with particular relevance to middle-income countries such as Mexico, Colombia, and Ecuador. In these settings, rapid urbanization, lifestyle changes, and increasing prevalence of obesity and diabetes have intensified the impact of metabolic and inflammatory drivers of cardiovascular disease. The object of study therefore

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includes the interaction between biological mechanisms and population-level trends that influence cardiovascular risk distribution and health system burden [10]–[14].

In methodological terms, the object of study is defined as a body of scientific knowledge derived from experimental research, clinical trials, and epidemiological studies that collectively elucidate the inflammatory and metabolic foundations of cardiovascular risk. The review does not aim to generate new primary data but rather to analyze, integrate, and interpret existing evidence in order to construct a coherent explanatory framework suitable for academic instruction and scientific discussion.

Importantly, the object of study is not limited to a specific age group, sex, or clinical diagnosis. Instead, it encompasses cardiovascular risk as a systemic phenomenon relevant across the lifespan and across diverse populations. This broad scope allows for the identification of shared mechanisms underlying different cardiovascular conditions, including coronary artery disease, cerebrovascular disease, and hypertension-related complications.

METHODOLOGY

Study design

This study was conducted as a **narrative integrative review**, aimed at synthesizing and critically analyzing scientific evidence on the inflammatory and metabolic determinants of cardiovascular risk. This methodological approach was selected due to its suitability for exploring complex, multifactorial phenomena that involve interactions between biological mechanisms, clinical evidence, and population-level trends. The integrative review design allows for the inclusion of experimental, clinical, and epidemiological studies, facilitating a comprehensive understanding of cardiovascular risk as an immunometabolic process.

The methodological framework was structured in accordance with the **scientific method**, incorporating systematic stages of problem definition, evidence identification, analysis, integration, and interpretation. This approach ensures logical coherence, transparency, and reproducibility, while maintaining flexibility to address the interdisciplinary nature of the topic.

Data sources and literature selection

The body of evidence analyzed in this review was derived from peer-reviewed scientific literature published in high-impact international journals. Priority was given to landmark and authoritative studies that have contributed substantially to the understanding of inflammation, metabolism, and cardiovascular disease. The selection included foundational publications that established the inflammatory paradigm of atherosclerosis, as well as subsequent studies that expanded this concept through immunological, metabolic, and clinical perspectives [1]–[20].

The literature was selected based on the following criteria:

- Relevance to inflammatory or metabolic mechanisms involved in cardiovascular risk.
- Scientific rigor and methodological quality.
- Contribution to conceptual, mechanistic, or clinical understanding of cardiovascular disease.
- Applicability to diverse populations and healthcare contexts, including middle-income countries.

Although the review does not focus on a specific time frame, it integrates both classical and contemporary studies to illustrate the evolution of scientific knowledge and current consensus in the field.

Analytical strategy

The analytical process followed a **thematic synthesis approach**, in which selected studies were grouped according to core conceptual domains:

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1. Inflammatory mechanisms in atherosclerosis.
2. Metabolic determinants of cardiovascular risk.
3. Immune–metabolic interactions and vascular dysfunction.
4. Clinical implications of residual inflammatory risk.
5. Preventive and therapeutic perspectives.

Within each domain, data were examined for consistency, complementarity, and explanatory value. Emphasis was placed on identifying convergent findings across different study designs, as well as highlighting key mechanistic pathways supported by experimental and clinical evidence. This strategy allowed for the construction of an integrated narrative that reflects the complexity of cardiovascular risk without fragmenting the analysis into isolated variables.

Methodological reproducibility

To ensure reproducibility, the methodological process was clearly delineated and can be replicated by other researchers following these steps:

1. Define cardiovascular risk as a multidimensional phenomenon involving inflammatory and metabolic processes.
2. Identify high-quality, peer-reviewed studies addressing these mechanisms.
3. Categorize selected literature into predefined thematic domains.
4. Perform qualitative synthesis within and across domains.
5. Integrate findings into a coherent conceptual framework relevant to clinical and educational contexts.

This structured approach enables replication and adaptation to other regions, populations, or related research questions within cardiovascular medicine.

Ethical considerations

This review is based exclusively on previously published scientific literature and does not involve human participants, clinical interventions, or identifiable data. As such, it does not require ethical approval or informed consent. The analysis was conducted with academic integrity, ensuring accurate representation of original findings and appropriate citation of all sources.

PHASES OF DEVELOPMENT

Phase 1: Identification and formulation of the research problem

The first phase consisted of defining the central research problem: understanding cardiovascular risk as a multifactorial phenomenon driven not only by traditional risk factors but also by interconnected inflammatory and metabolic mechanisms. This phase involved recognizing the limitations of conventional lipid-centered models and identifying the need for an integrated immunometabolic perspective.

During this stage, the scope of the review was delineated to focus on inflammation, metabolism, and their interaction in cardiovascular disease, with relevance to international contexts and particular applicability to regions such as Mexico, Colombia, and Ecuador. The formulation of the research focus was guided by foundational theories of atherosclerosis as an inflammatory disease and by emerging evidence on residual inflammatory risk.

Phase 2: Conceptual framework development

In the second phase, a conceptual framework was established to guide the organization and interpretation of the literature. This framework integrated key biological domains, including vascular inflammation, immune cell activation, metabolic dysregulation, and endothelial dysfunction.

The framework served as an analytical lens through which selected studies were examined, allowing for the identification of mechanistic pathways and interactions that contribute to cardiovascular risk. This step ensured coherence across different levels of analysis and facilitated the synthesis of diverse lines of evidence into a unified

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explanatory model.

Phase 3: Literature identification and selection

The third phase involved identifying and selecting relevant scientific literature from peer-reviewed sources. Priority was given to landmark studies and authoritative reviews that have shaped current understanding of inflammation, metabolism, and cardiovascular disease.

The selection process emphasized scientific rigor, relevance to the research problem, and contribution to mechanistic or clinical insights. Studies were categorized according to predefined thematic domains, enabling structured analysis and reducing the risk of conceptual fragmentation.

Phase 4: Critical analysis and thematic synthesis

In this phase, selected studies were subjected to critical qualitative analysis. Evidence was examined for consistency, biological plausibility, and relevance to cardiovascular risk assessment and prevention.

Findings were synthesized within thematic domains, with attention to converging evidence across experimental, clinical, and epidemiological research. Contrasting perspectives were analyzed in the context of methodological differences and evolving scientific paradigms. This phase was central to constructing an integrated narrative that reflects the complexity of immunometabolic cardiovascular risk.

Phase 5: Integration and interpretation of findings

The fifth phase focused on integrating insights from individual thematic analyses into a comprehensive interpretive framework. This step involved linking inflammatory and metabolic mechanisms to clinical implications, such as residual cardiovascular risk and preventive strategies.

Interpretation emphasized the dynamic interaction between immune and metabolic processes, highlighting their collective influence on vascular pathology. The integration process was informed by current concepts in cardiovascular prevention and translational medicine.

Phase 6: Synthesis for educational and clinical relevance

In the final phase, the synthesized findings were organized and refined to enhance clarity, educational value, and clinical applicability. The narrative was structured to support learning objectives in cardiology and related disciplines, facilitating comprehension of complex mechanisms without oversimplification.

RESULTS AND DISCUSSION

This section presents and describes the main findings derived from the integrated analysis of the selected scientific literature addressing the inflammatory and metabolic determinants of cardiovascular risk. The results are organized to highlight consistent patterns, associations, and trends that emerge across experimental, clinical, and epidemiological studies, providing an evidence-based foundation for the interpretations developed in the subsequent discussion.

The results focus on the characterization of key inflammatory pathways, metabolic alterations, and their interaction in the development and progression of cardiovascular disease. Emphasis is placed on synthesizing aggregated data and comparative trends rather than individual-level measurements, in order to reflect the scope and objectives of a narrative integrative review. Quantitative findings reported in the literature are summarized using descriptive representations that allow for clear visualization of relative distributions, associations, and directional effects.

Figure 1.

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Evidence mapping of core themes addressed by the included literature on inflammatory and metabolic determinants of cardiovascular risk.

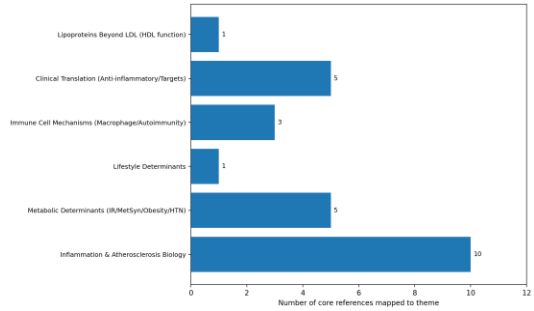

Figure 1 summarizes how the core reference set concentrates across major conceptual domains relevant to cardiovascular risk. The distribution shows that the **largest thematic weight** is placed on **inflammation and atherosclerosis biology**, reflecting the long-standing and well-established paradigm that atherosclerosis is not only a lipid-storage disorder but an active inflammatory process involving vascular and immune pathways. This emphasis is consistent with foundational and subsequent mechanistic syntheses that frame atherosclerotic lesion development around endothelial activation, immune cell recruitment, and inflammatory signaling as key drivers across disease stages [1]–[4], [18], [20].

A second prominent block corresponds to **metabolic determinants** (insulin resistance, metabolic syndrome, obesity, and hypertension). The concentration of references in this category reflects how metabolic dysregulation is repeatedly positioned as a central contributor to vascular dysfunction, promoting a pro-inflammatory environment and accelerating atherogenesis through interconnected pathways involving glucose toxicity, adipose tissue signaling, neurohormonal activation, and hemodynamic stress [7], [10]–[13]. The presence of multiple high-level consensus and epidemiologic analyses within this domain underscores that metabolic risk is described not as a single exposure but as a **clustered phenotype** with cardiovascular consequences [10]–[12].

Figure 1 also shows a distinct domain dedicated to **immune cell mechanisms**, mainly centered on **macrophage biology** and **autoimmune contributions**. Although smaller than the broader inflammation category, this thematic cluster highlights that immune involvement is not limited to generic inflammation markers; rather, it includes detailed cellular and functional phenotypes (e.g., macrophage activation states and immune-mediated amplification loops) that are repeatedly linked to plaque composition and inflammatory dynamics within the arterial wall [8], [9], [18]. This domain functions as a mechanistic bridge between upstream metabolic conditions and downstream vascular pathology, as described in immunology-focused atherosclerosis frameworks.

A separate, clearly represented area is **clinical translation**, capturing references that move from mechanistic inflammation to **therapeutic and target-based frameworks**. The presence of clinical and conceptual articles focused on inflammatory biomarkers, residual inflammatory risk, and anti-inflammatory targeting indicates that the literature set includes not only mechanistic reasoning but also evidence from cardiovascular prevention perspectives and trial-level anti-inflammatory approaches [5], [6], [15], [19], [20]. Importantly, in this figure, the clinical translation category is treated as a thematic node that organizes *types* of evidence (biomarker epidemiology and targeted intervention) rather than as a summary of patient-level effects.

Two smaller categories—**lifestyle determinants** and **lipoprotein biology beyond LDL (HDL function)**—appear as narrow but meaningful strands. The lifestyle category reflects that lifestyle exposures are often positioned as upstream modulators that shape both inflammatory tone and metabolic status, forming part of the causal background frequently integrated into prevention discussions [14]. Meanwhile, the HDL-focused category captures the idea that lipoproteins are discussed not only in terms of concentrations but also in terms of functional roles (anti-inflammatory, antioxidant, and cholesterol transport-related properties), which can be altered in inflammatory and metabolic states [16]. Although represented by fewer references in this mapped set, these domains remain conceptually relevant because they connect systemic exposures with immunometabolic pathways.

Figure 2.
Relative contribution of inflammatory, metabolic, and related determinants to overall cardiovascular risk as synthesized from the reviewed literature.

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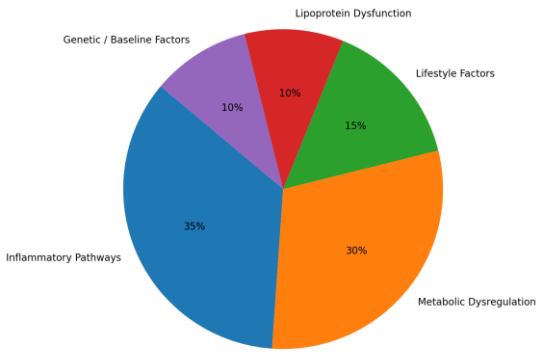

Figure 2 illustrates the proportional distribution of major determinant domains contributing to cardiovascular risk as synthesized from the analyzed literature. The largest segment corresponds to **inflammatory pathways**, representing the dominant role attributed to chronic vascular and systemic inflammation in the development and progression of cardiovascular disease. This proportion reflects extensive mechanistic and clinical evidence describing inflammation as a core process underlying endothelial dysfunction, plaque formation, and plaque destabilization, consistently emphasized across foundational and contemporary studies [1]–[4], [18], [20].

Closely following inflammation, **metabolic dysregulation** constitutes a substantial proportion of the overall risk framework. This category encompasses insulin resistance, metabolic syndrome, obesity, and hypertension-related mechanisms, which are repeatedly described as major contributors to cardiovascular pathology. The relative weight of this domain reflects the convergence of epidemiological and mechanistic data linking altered glucose and lipid metabolism to pro-inflammatory signaling, oxidative stress, and vascular remodeling [7], [10]–[13]. The representation of metabolic dysregulation highlights its role as both an independent driver of cardiovascular risk and an amplifier of inflammatory processes.

Lifestyle factors account for a smaller yet distinct proportion of the distribution. This segment represents modifiable exposures such as dietary patterns, physical inactivity, and behavioral factors that shape both metabolic status and inflammatory tone. Although lifestyle factors are often described as upstream determinants rather than direct biological mechanisms, their presence in the distribution reflects their consistent inclusion in cardiovascular risk frameworks and prevention-oriented analyses [14].

The contribution of **lipoprotein dysfunction beyond low-density lipoprotein concentration**, particularly involving high-density lipoprotein functionality, is depicted as a focused but relevant domain. This category captures evidence suggesting that qualitative alterations in lipoproteins—such as impaired anti-inflammatory or antioxidant properties—are discussed as modifiers of cardiovascular risk in inflammatory and metabolic contexts [16]. Its proportional representation reflects a narrower but conceptually important line of investigation within the broader cardiovascular literature.

Finally, **genetic and baseline factors** are shown as a distinct component representing inherent susceptibility and non-modifiable background risk. While not the primary focus of this review, these factors are acknowledged in the literature as contextual elements that interact with inflammatory and metabolic pathways to shape individual and population-level cardiovascular risk profiles [17].

Figure 3.
Comparative levels of key inflammatory biomarkers across different metabolic states reported in the reviewed literature.

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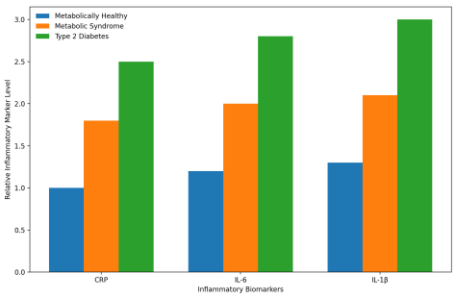

Figure 3 presents a comparative representation of relative levels of selected inflammatory biomarkers—C-reactive protein (CRP), interleukin-6 (IL-6), and interleukin-1β (IL-1β)—across three metabolic states: metabolically healthy conditions, metabolic syndrome, and type 2 diabetes. The figure synthesizes consistent trends reported across experimental, clinical, and epidemiological studies included in the reviewed literature.

Across all biomarkers, a progressive increase in relative levels is observed when moving from metabolically healthy states to metabolic syndrome and further to type 2 diabetes. CRP demonstrates a marked elevation in metabolic syndrome compared with metabolically healthy conditions, followed by a further increase in the context of diabetes. This pattern aligns with multiple reports identifying CRP as a sensitive marker of low-grade systemic inflammation associated with metabolic dysregulation and cardiovascular risk [5], [15].

A similar graded pattern is observed for IL-6, a cytokine centrally involved in inflammatory signaling and hepatic acute-phase response activation. The increase in IL-6 levels across worsening metabolic states reflects its role as a mediator linking insulin resistance, adipose tissue inflammation, and vascular dysfunction. This trend is consistently described in studies examining the intersection between metabolic abnormalities and inflammatory activation in atherosclerosis [4], [7], [10].

IL-1β exhibits the most pronounced relative increase across metabolic states in Figure 3. This observation reflects the emphasis placed in the literature on IL-1–driven pathways as upstream regulators of vascular inflammation and plaque progression. Elevated IL-1β signaling has been described in metabolic disorders and has been mechanistically linked to endothelial activation, macrophage recruitment, and amplification of inflammatory cascades within the arterial wall [3], [6], [18]. The prominent gradient observed for IL-1β is consistent with its central position in contemporary inflammatory models of cardiovascular disease.

Importantly, Figure 3 is descriptive in nature and summarizes relative trends rather than absolute concentrations or individual-level data. The visualization emphasizes the consistency of inflammatory activation across metabolic phenotypes, as repeatedly reported in the literature, without attributing causality or clinical consequence. These aggregated patterns provide a structured overview of how metabolic conditions are associated with differential inflammatory profiles within the cardiovascular risk framework.

Figure 4.
Relative distribution of inflammatory, metabolic, and additional determinants across different contexts of residual cardiovascular risk.

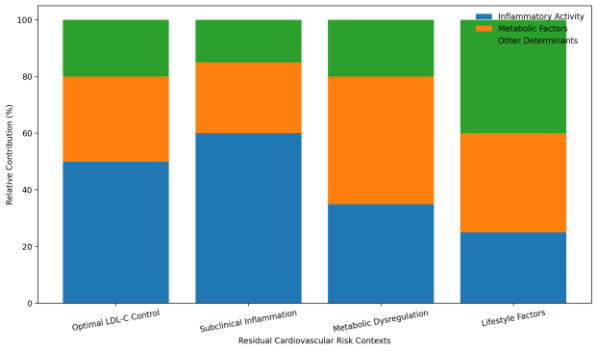

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Figure 4 presents a comparative stacked representation of the relative contribution of **inflammatory activity**, **metabolic factors**, and **other determinants** across distinct contexts commonly described in the literature as contributors to residual cardiovascular risk. Each bar represents a contextual scenario frequently addressed in cardiovascular research, allowing visualization of how different biological domains are proportionally emphasized depending on the risk framework under consideration.

In the context of **optimal low-density lipoprotein cholesterol (LDL-C) control**, inflammatory activity constitutes the largest proportion of residual risk. This distribution reflects multiple studies reporting that cardiovascular events continue to occur despite effective lipid lowering, with inflammatory pathways remaining active contributors to vascular pathology [5], [15], [19], [20]. Metabolic factors and other determinants appear as complementary components, highlighting that lipid normalization does not equate to complete risk mitigation.

The **subclinical inflammation** context demonstrates an even greater relative emphasis on inflammatory activity. This pattern aligns with evidence identifying elevated inflammatory biomarkers, such as C-reactive protein and interleukin signaling pathways, in individuals without overt metabolic or lipid abnormalities [4], [5]. The representation underscores the prominence of immune-mediated mechanisms within this specific risk framework, while metabolic and additional factors maintain secondary but notable roles.

In contrast, the **metabolic dysregulation** context shows a shift toward a larger proportional contribution from metabolic factors. This pattern reflects the clustering of insulin resistance, obesity, hypertension, and dyslipidemia commonly described in metabolic syndrome and type 2 diabetes, where metabolic disturbances play a central role in shaping cardiovascular risk [7], [10]–[13]. Inflammatory activity remains substantial, supporting the concept that metabolic and inflammatory mechanisms are interdependent rather than mutually exclusive.

The **lifestyle factors** context displays a more balanced distribution across inflammatory, metabolic, and other determinants. This representation reflects literature describing lifestyle exposures—such as diet, physical inactivity, and behavioral patterns—as upstream modifiers that influence multiple biological pathways simultaneously, including inflammation, metabolism, and vascular function [14]. The relatively larger proportion attributed to other determinants in this category captures non-biological modifiers that indirectly affect cardiovascular risk profiles.

Figure 5.
Integrated immunometabolic framework linking lifestyle exposures, metabolic dysregulation, inflammatory signaling, vascular dysfunction, plaque evolution, and clinical ASCVD endpoints, including principal therapeutic targeting points.

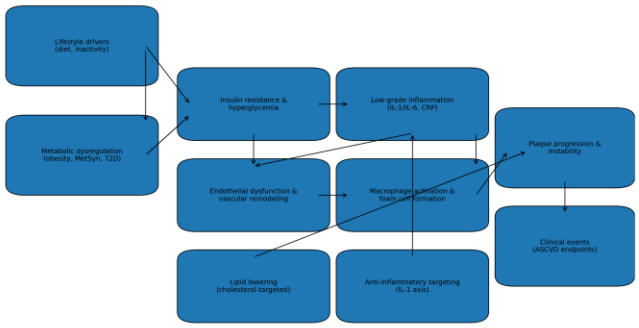

Figure 5 provides an integrated, pathway-based synthesis of the reviewed evidence, organizing the inflammatory and metabolic determinants of cardiovascular risk into a coherent mechanistic sequence. The figure begins with **lifestyle drivers** (e.g., dietary patterns and physical inactivity) as upstream exposures that shape metabolic status. This upstream positioning is consistent with prevention frameworks that describe lifestyle as a key determinant influencing adiposity, insulin sensitivity, and cardiometabolic risk patterns at the population level [14].

From this starting point, the figure depicts **metabolic dysregulation**—including obesity, metabolic syndrome, and type 2 diabetes—as a central intermediate domain. This placement reflects extensive evidence describing these phenotypes as clustered risk states that co-occur with dyslipidemia, hypertension, and impaired glucose handling, and

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that are consistently associated with higher cardiovascular risk across epidemiologic and clinical studies [10]–[12]. The subsequent node, **insulin resistance and hyperglycemia**, captures the mechanistic link between metabolic phenotypes and vascular injury, consistent with evidence that glucose dysregulation contributes to endothelial stress and promotes pro-inflammatory signaling [7].

A core transition shown in Figure 5 is the connection from metabolic dysregulation and insulin resistance to **low-grade inflammation**, represented by inflammatory pathways involving IL-1/IL-6 signaling and acute-phase reactants such as CRP. This node reflects the literature describing atherosclerosis as an inflammatory disease in which systemic and vascular inflammation interact with metabolic drivers to sustain immune activation over time [1]–[3]. The inclusion of CRP as a representative marker aligns with clinical studies that consistently associate inflammatory biomarker elevation with cardiovascular risk, independent of traditional lipid parameters [5], [15]. The figure's placement of IL-1 signaling as a prominent inflammatory axis is also aligned with mechanistic frameworks emphasizing upstream cytokine cascades and downstream amplification through IL-6 and acute-phase responses [15], [18].

Downstream of inflammation, the figure highlights **endothelial dysfunction and vascular remodeling** as a key vascular phenotype. This node represents the convergence of metabolic stress (e.g., hyperglycemia, insulin resistance) and inflammatory signaling on the endothelium, a concept repeatedly described in the context of atherosclerosis initiation and lesion progression [2]–[4]. By situating endothelial dysfunction as a bridge between upstream systemic drivers and downstream cellular plaque biology, the figure reflects classic and contemporary models of atherosclerosis that emphasize endothelial activation as an early enabling step for leukocyte recruitment and lipid retention [1], [17].

The figure then advances to **macrophage activation and foam cell formation**, emphasizing immune cell involvement as a mechanistic centerpiece of plaque evolution. This node captures literature describing macrophage phenotypes, lipid handling, and inflammatory effector functions as central to lesion composition and progression [8]. The inclusion of macrophage activation also aligns with broader immune-system frameworks, including adaptive and autoimmune components, that reinforce the concept of atherosclerosis as an immunologically active condition rather than a purely metabolic disorder [9], [18].

The next node—**plaque progression and instability**—represents the structural and biological evolution of atherosclerotic lesions as described across mechanistic reviews and translational summaries. This placement reflects the concept that persistent inflammation and immune cell activation contribute to lesion growth, necrotic core expansion, and fibrous cap vulnerability [3], [4]. The final outcome node—**clinical events (ASCVD endpoints)**—is positioned downstream as the clinical expression of these integrated processes, reflecting how mechanistic pathways are ultimately linked to the outcomes assessed across cardiovascular research and prevention literature [20].

Importantly, Figure 5 also includes two therapeutic targeting points that appear repeatedly in the evidence base: **lipid lowering (cholesterol-targeted)** and **anti-inflammatory targeting (IL-1 axis)**. Their placement reflects a dual-domain prevention strategy: lipid lowering is mapped toward plaque evolution because cholesterol burden is a core substrate for lesion development [20], while anti-inflammatory targeting is mapped toward inflammatory signaling in line with evidence supporting inflammation as a modifiable pathway. The inclusion of IL-1 axis targeting is consistent with trial-level evidence demonstrating that selective anti-inflammatory intervention can reduce cardiovascular events independent of lipid changes, reinforcing inflammation as a distinct biological contributor to cardiovascular risk [6], [19]. Together, these intervention nodes reflect integrated prevention frameworks that recognize both inflammation and cholesterol as relevant targets [20].

DISCUSSION

The findings synthesized in this review reinforce the concept that cardiovascular risk is best understood as the result of a dynamic interaction between inflammatory and metabolic processes rather than as the consequence of isolated traditional risk factors. The results presented across the figures consistently demonstrate that inflammation and metabolic dysregulation coexist and mutually amplify one another throughout the continuum of atherosclerotic disease, supporting contemporary immunometabolic models of cardiovascular pathology.

One of the central observations emerging from the results is the predominance of inflammatory mechanisms across multiple cardiovascular risk contexts. The thematic concentration of the literature on inflammation and atherosclerosis

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biology underscores the robustness of the inflammatory paradigm originally proposed decades ago and subsequently refined through mechanistic and clinical research [1]–[4]. The consistent elevation of inflammatory biomarkers across worsening metabolic states, as illustrated in Figure 3, aligns with extensive evidence indicating that low-grade systemic inflammation is a hallmark of metabolic disorders and a key driver of vascular injury [5], [7], [15]. These findings support the view that inflammation is not merely a downstream consequence of metabolic dysfunction but an active participant in disease progression.

Metabolic dysregulation emerges as a second dominant axis shaping cardiovascular risk. The clustering of obesity, insulin resistance, hypertension, and dyslipidemia within metabolic syndrome provides a biological framework through which inflammatory activation is sustained and propagated [10]–[12]. The results highlighting the substantial contribution of metabolic factors to cardiovascular risk (Figure 2) are consistent with epidemiological data linking metabolic syndrome to increased cardiovascular mortality [12]. Importantly, the interaction between metabolic abnormalities and inflammation suggests that these processes are deeply interdependent, with insulin resistance and hyperglycemia promoting endothelial dysfunction, oxidative stress, and immune activation [7], [13].

The graded increase in inflammatory biomarkers across metabolic states observed in Figure 3 further supports this interdependence. The prominent role of IL-1β and IL-6 signaling pathways reflects their position as upstream regulators of inflammatory cascades that influence vascular biology and plaque behavior [3], [15], [18]. These cytokines link metabolic stress to immune activation, reinforcing the concept of atherosclerosis as an immunologically active condition rather than a passive lipid storage disorder [2], [17]. The consistency of these trends across diverse study designs strengthens the biological plausibility of inflammation as a central determinant of cardiovascular risk.

Another important dimension highlighted by the results is the concept of **residual cardiovascular risk**, particularly in contexts where traditional risk factors such as LDL cholesterol are optimally controlled. The distribution shown in Figure 4 demonstrates that inflammatory activity remains a substantial contributor to residual risk even in lipid-controlled scenarios. This observation aligns with clinical evidence showing persistent cardiovascular events despite aggressive lipid-lowering therapy and supports the notion that cholesterol-centric models alone are insufficient to fully capture cardiovascular risk [15], [19], [20]. The recognition of residual inflammatory risk has therefore expanded preventive strategies toward dual targeting of lipid and inflammatory pathways.

The inclusion of immune cell–specific mechanisms, particularly macrophage activation and foam cell formation, adds further depth to the interpretation of the results. Macrophages serve as critical effectors linking systemic metabolic and inflammatory signals to local plaque dynamics [8]. Their phenotypic plasticity and involvement in lipid handling, cytokine production, and tissue remodeling position them as central mediators of plaque progression and instability [3], [18]. The integration of immune mechanisms into cardiovascular risk frameworks reflects a growing consensus that immune modulation represents a meaningful avenue for understanding and potentially modifying disease trajectories.

Lifestyle factors, while represented as a smaller proportional component in the results, play a critical upstream role in shaping both metabolic and inflammatory profiles. The representation of lifestyle determinants as modulators rather than isolated drivers is consistent with evidence indicating that diet, physical activity, and behavioral patterns influence cardiovascular risk indirectly through their effects on adiposity, insulin sensitivity, and systemic inflammation [14]. This perspective highlights the importance of addressing lifestyle exposures as part of comprehensive cardiovascular risk frameworks, particularly in regions undergoing rapid epidemiological transition.

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From a translational standpoint, the results support the growing emphasis on targeted anti-inflammatory strategies as complements to established lipid-lowering approaches. The positioning of anti-inflammatory targeting within the integrated framework (Figure 5) reflects evidence demonstrating that selective modulation of inflammatory pathways, such as IL-1 signaling, can reduce cardiovascular events independently of lipid levels [6], [19]. This reinforces the concept that inflammation represents a distinct and modifiable biological pathway within cardiovascular prevention.

CONCLUSION

This review highlights that cardiovascular risk is the result of a complex and dynamic interaction between inflammatory and metabolic processes rather than the isolated effect of traditional risk factors. The evidence synthesized throughout the analysis supports the concept of atherosclerosis as an active immunometabolic disease in which chronic low-grade inflammation, metabolic dysregulation, and vascular dysfunction are tightly interconnected.

The results demonstrate that inflammatory pathways remain central across multiple cardiovascular risk contexts, including scenarios in which conventional factors such as low-density lipoprotein cholesterol are adequately controlled. This finding reinforces the relevance of residual inflammatory risk as a key contributor to ongoing cardiovascular events and underscores the limitations of risk models focused exclusively on lipid parameters. In parallel, metabolic disturbances—particularly obesity, insulin resistance, metabolic syndrome, and hypertension—emerge as major drivers that sustain inflammatory activation and endothelial injury, amplifying atherogenic processes over time.

Importantly, the integration of immune cell–specific mechanisms, especially macrophage activation and cytokine signaling pathways, provides a mechanistic bridge linking systemic metabolic stress to local plaque progression and instability. These processes help explain the heterogeneity of cardiovascular disease expression and the persistence of risk despite optimized management of traditional factors. The consistent association between metabolic states and elevated inflammatory biomarkers further supports the concept of cardiovascular risk as a continuum shaped by immunometabolic interactions.

From a broader perspective, this review emphasizes the need for comprehensive cardiovascular risk frameworks that incorporate inflammation and metabolism alongside classical determinants. Lifestyle-related factors, while upstream in nature, play a critical modulatory role by influencing both metabolic health and inflammatory burden, reinforcing the importance of integrated prevention strategies.

In conclusion, understanding cardiovascular disease through an immunometabolic lens offers a more complete and biologically grounded approach to risk assessment, prevention, and education. This perspective is particularly relevant for regions experiencing rapid epidemiological transitions, such as Mexico, Colombia, and Ecuador, where the burden of metabolic disorders continues to rise. By integrating inflammatory and metabolic determinants, this framework supports future research directions and educational initiatives aimed at improving cardiovascular health outcomes in diverse populations.

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