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Global Research Trends in the Use of Apolipoprotein E Deficient Mouse Models for Atherosclerosis: A Bibliometric Analysis

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Abstract

ApoE-deficient mice are among the most commonly used experimental models for investigating atherosclerosis. Despite more than three decades of extensive research, a comprehensive global overview of the scientific landscape surrounding this model remains limited. Thus, the objective of the study was to conduct a bibliometric analysis to assess global research trends, impactful publications and emerging thematic focus in research using this mouse model in atherosclerosis. The Web of Science and Scopus databases were searched to retrieve publications. Subsequent screening and filtering yielded 3,263 original research articles published between 1992 and 2025. ScientoPy (v2.1.3) was used to create bibliometric indicators for publication trends, citation metrics and journal productivity, whereas VOSviewer (v1.6.20) was used to visualize keyword co-occurrence and thematic clusters. The findings indicate a high level of scientific productivity, with a relatively stable publication rate over the last ten years. China and the United States were the most notable contributors, accounting for a significant share of global research output. Arteriosclerosis, Thrombosis and Vascular Biology and Atherosclerosis were the most productive journals, with most publications in first-quartile cardiovascular journals. Citation analysis revealed landmark studies in which the mouse served as a primary model for lipid metabolism, vascular remodeling and immune signaling. Eight major thematic clusters were identified: cardiometabolic diseases, macrophage-driven lipid metabolism, vascular remodeling, oxidative stress, plaque stability, immune regulation, microbiome interactions and therapeutic strategies. This bibliometric analysis demonstrates that research on ApoE-deficient mice constitutes a mature, globally collaborative scientific domain, with a shift from lipid-focused to broader mechanisms, including immunometabolism and interactions with the gut microbiota.

Keywords: ApoE-deficient Mice, Atherosclerosis, Bibliometric Analysis, Experimental Model.

Introduction

Cardiovascular Disease (CVD) is the primary cause of morbidity and mortality worldwide and atherosclerosis is the pathological process that underlies the catastrophic event of a myocardial infarction and stroke (1). Atherosclerosis is a complex, chronic inflammatory condition that involves a series of interrelated events, such as the deposition of lipids under the endothelium, endothelial dysfunction and the recruitment of inflammatory cells (2). The progression of these cellular mechanisms will result in progressive fibrofatty plaques. The rupture of these plaques can lead to acute thrombotic events and significant clinical complications. Atherosclerosis was originally regarded as a disease of excess lipids and cholesterol in the arterial wall. Recent advances in cardiac research have shifted this perspective, recognizing atherosclerosis as a multifactorial disease in which lipids, inflammation, immune function, endothelial dysfunction, oxidative stress and vascular remodeling play roles. Recently, studies have been expanded to explore the role of systemic metabolic disorders, gut microbiota-host interactions and other integrative biological mechanisms in disease progression (3). The developments have contributed to the growing body of literature and the need for robust experimental models to investigate various aspects of atherosclerosis pathogenesis. Given the interplay of atherosclerosis pathogenesis, experimental animal models are crucial for understanding these pathogenic pathways and evaluating therapeutic approaches (4).

The Apolipoprotein E-deficient (ApoE-deficient or

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ApoE^{-}/$^{-}$) mouse has become one of the most widely used models for studying the pathophysiology of atherosclerosis. This model was developed by targeted homologous recombination in embryonic stem cells and indicated that the lack of ApoE results in severe hypercholesterolemia and that atherosclerotic lesions form spontaneously, even in the absence of dietary changes (5). This discovery defined a new paradigm of genetics that represents important human pathological mechanisms of atherosclerosis. It was also demonstrated that ApoE-deficient mice exhibit all stages of atherosclerosis, ranging from early fatty streaks to late fibrous plaques with necrotic cores (6). Therefore, the ApoE-deficient mouse has become one of the most important models for investigating the molecular and cellular pathophysiology of vascular disease (4).

Early research on the ApoE-deficient model of atherosclerosis focused on lipid metabolism and lesion development and more recent studies have expanded into the broader field of vascular biology, including immune regulation, oxidative stress, endothelial damage, extracellular matrix (ECM) remodeling and thrombosis. The model has provided insights into mechanisms of inflammation, cholesterol transport pathways, cytokine signaling pathways and mechanisms involved in plaque progression and stability. In addition, ApoE-deficient mice have become a useful model for testing novel pharmacological, dietary, genetic and cell-based therapeutic strategies to reduce cardiovascular risk (2).

Many narrative reviews and experimental overviews have discussed the biological properties and the application of ApoE-deficient mice in cardiovascular research. Previously, the model has been validated for mimicking hypercholesterolemia, vascular wall inflammation, endothelial dysfunction and progressive plaque development (7, 8). Other studies have also compared ApoE-deficient mice with other models, such as LDL receptor-deficient and diet-induced atherosclerosis models (9, 10), underscoring their utility for mechanistic studies and as preclinical tools to assess therapeutic interventions. All these publications have contributed significantly to the understanding of the strengths, limitations and translatability of ApoE-deficient mice in atherosclerosis research. Such reviews, however, focused mainly on summarizing biological results and experimental applications, rather than quantitatively assessing the development of the research area.

Over the past three decades, ApoE-deficient mice have been studied extensively and have been the subject of thousands of publications. Yet, the intellectual framework and trajectory of this research field remain poorly understood. Many reviews have been dedicated to the biological mechanisms, disease progression, or therapeutic outcomes, but no bibliometric analyses have examined the entire scientific field of ApoE-deficient mouse models of atherosclerosis. It remains unknown how the field has evolved over the years, which countries have contributed most significantly to the field, which publications have been seminal for current understanding and how the thematic priorities have shifted from the classical lipid metabolism to broader themes like the interaction of microbiome, immune regulation, vascular remodeling and precision therapeutics.

Bibliometric analysis offers a systematic and quantitative methodology for evaluating the development of scientific fields. Unlike narrative reviews, bibliometric reviews allow the evaluation of publication productivity, impact, collaborative networks and the development of themes in a large volume of publications (11). Citation analysis and keyword co-occurrence mapping can be used in bibliometric studies to identify key publications, research trends and the development of knowledge within a given research domain. These methods are especially helpful in more established research fields, where thousands of papers have been published in the last few decades.

While there have been previous bibliometric studies on wider aspects of ApoE research, including highly cited ApoE publications and the application of ApoE in Alzheimer's disease, none have specifically addressed the ApoE-deficient mouse models used in atherosclerosis studies. One previous bibliometric study conducted a citation analysis of the 100 most influential papers on ApoE and found that research on ApoE has had a significant scientific impact across several biomedical fields, including Alzheimer's disease, lipid metabolism and cardiovascular biology (12). Likewise, another study conducted a bibliometric analysis of global research on the role of ApoE in Alzheimer's disease and identified key

contributors, influential institutions and emerging themes in biomarkers, genetic risk and disease mechanisms (13). These studies emphasized the importance of bibliometric approaches for analyzing the evolution of scientific research on ApoE, but did not evaluate the global research landscape of ApoE-deficient mouse models in atherosclerosis.

To our knowledge, this is the first comprehensive bibliometric analysis specifically focused on ApoE-deficient mice in atherosclerosis research, quantifying trends in publications, influential contributors and the development of topics in scientific research on these models. Using a bibliometric approach, the impact of this influential experimental model on current research on cardiovascular diseases can be systematically assessed by examining research output, citations, geographical contributions, influential journals, key publications and the evolution of field themes. To address this gap, the purpose of the current study is to thoroughly characterize the global research landscape of ApoE-deficient mouse models in atherosclerosis via bibliometric analysis. In particular, this paper aims to:

a) examine publication and citation trends over time;
b) identify the most productive countries and highlight the major journals in this field;
c) investigate the conceptual and thematic organization of the literature through citation analysis and keyword co-occurrence mapping; and
d) identify emerging research hotspots and future research directions.

This study will clarify the dynamics of research on ApoE-deficient mice by identifying influential publications, leading countries and journals and emerging research themes. The results could help researchers identify new directions for investigation, inform further experimental studies and help funding agencies and policymakers recognize emerging priorities in atherosclerosis research.

Methodology

A comprehensive bibliometric mapping was conducted to assess the evolution of research on the ApoE-deficient mouse model in atherosclerosis. The search strategy was predesigned and applied to the two databases, Scopus and Web of Science, on 15 February 2026, using the keywords “apolipoprotein E”, “ApoE knockout” and “mouse model”, together with “atherosclerosis” or “atherogenesis”. The publications screened were published between January 1992 and December 2025.

Data eligibility was based on a strict inclusion framework. Only original research articles involving the ApoE-deficient mouse models were included in the analysis. To ensure reliability of the bibliometric indicators, reviews, editorial materials and conference abstracts were excluded. In addition, only English-language publications have been selected for the dataset to standardize citations and the analysis of word co-occurrence. The screening process was conducted manually by two independent reviewers according to the predefined inclusion and exclusion criteria. The discrepancies regarding study eligibility were resolved through discussion and consensus.

Figure 1 shows that the first search yielded 7,320 records, of which 2,675 were in Scopus and 4,645 were in the Web of Science Core Collection. A total of 2,327 duplicate records were identified and removed using the ScientoPy (v2.1.3) bibliometric framework. This resulted in 4,993 unique records being retained for subsequent application of a screening filtering process. A total of 1,583 non-article publications, including editorials and conference proceedings, were removed, along with 147 non-English documents. Based on these criteria, 3,263 original research articles were included in the final dataset.

The data were then analyzed using a multidimensional bibliometric approach to identify trends in publications over time, the national contribution of the research and journal productivity using ScientoPy (version 2.1.3). Furthermore, descriptive bibliometric indicators, citation impact analysis and keyword co-occurrence mapping were applied using VOSviewer (version 1.6.20) to analyze the conceptual framework and thematic development of the research field.

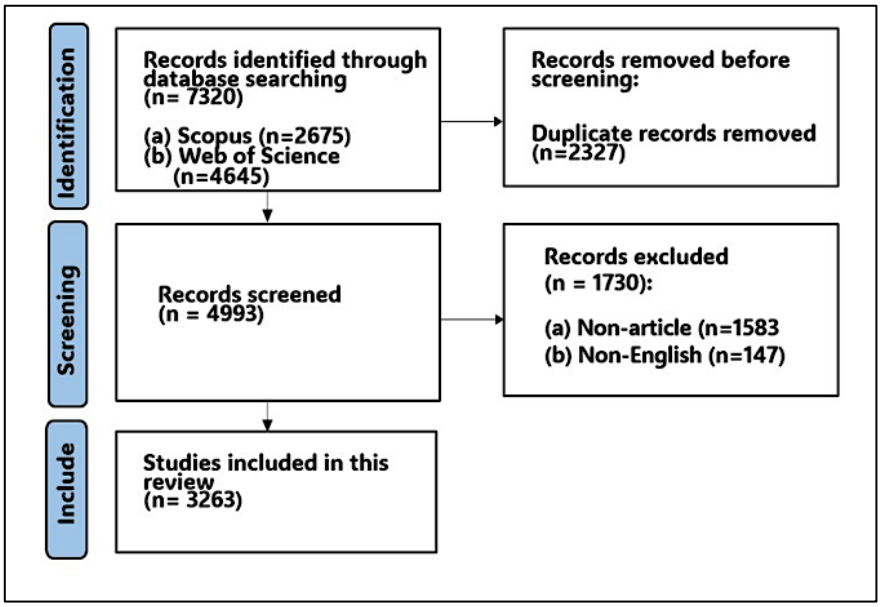

Figure 1: Flowchart of the Screening Process (14)

Results

Publication Trends

Figure 2 shows the publication trends in ApoE-deficient mice in atherosclerosis research. It demonstrates that temporal distribution analysis indicates that ApoE-deficient mouse studies in atherosclerosis research have followed a pattern of vigorous, steady research activity over the past decade. The 2016-2019 timeframe was characterized by steady annual academic output, ranging from 153 to 174 original articles, demonstrating continuous interest in this experimental model among the vascular biology community. Such sustained scientific interest is largely due to the model's established experimental usefulness. The ApoE-deficient mouse spontaneously develops severe hypercholesterolemia and progressive atherosclerotic lesions without further genetic or dietary treatment. Such an attribute provides scientists with a highly standardized, reproducible system for exploring the complex pathways underlying lipid metabolism, vascular inflammation and atherosclerotic lesion formation (4).

Academic production during 2020-2022 was at a plateau, with yearly publications ranging from 149 to 155 articles, indicating that ApoE-deficient mouse studies have reached a stage of methodological maturity. With its evolution beyond the early days of model validation, this well-developed framework is now being employed by the scientific community as a generalized platform of higher-order questions, such as mechanistic refinement, assessment of new therapeutic interventions and translational modeling. These stabilization patterns are typical of mature scientific fields with established methodologies that have achieved high levels of consensus and extensive use (15).

The volume of publications declined after 2023, with 123 articles in 2024 and 118 in 2025. This apparent downward trend, however, must be viewed with some caution. The reduced numbers are probably due to delays in bibliographic indexing and citation lag, rather than a decline in research activity. Newly published research works can take time to be fully indexed in major databases such as Scopus and Web of Science. Consequently, the number of publications in recent years might be artificially reduced. This limitation is frequently encountered in longitudinal bibliometric studies, where data completeness depends on the database's update cycle.

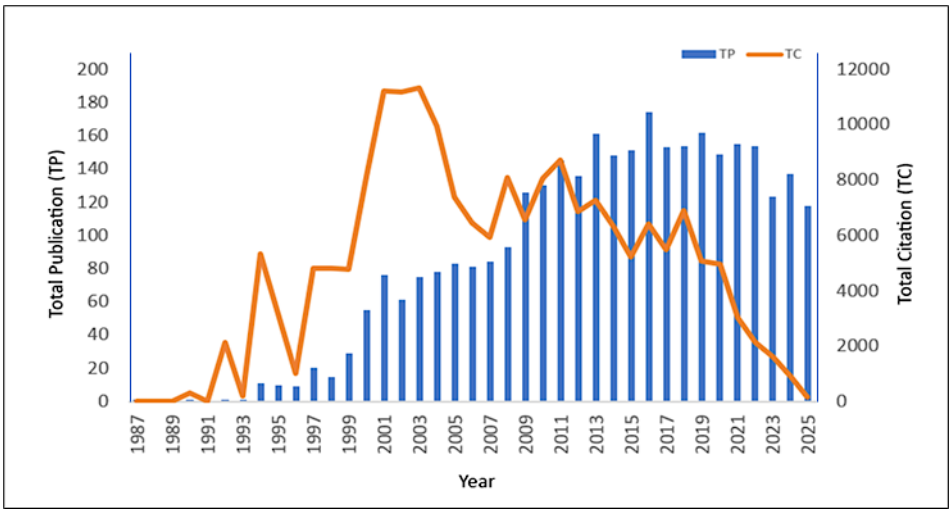

Figure 2: The Publication Trends in ApoE-deficient Mouse in Atherosclerosis Research

Country and Regional Contributions

Figure 3 demonstrates the top 10 most productive countries in ApoE-deficient mouse atherosclerosis research. It shows that the geographic landscape of ApoE-deficient mouse research has an extremely concentrated architecture of scientific productivity. The two main pillars of the field are China and the United States, which account for 1,070 and 1,034 publications, respectively. Their overall leadership underscores their pivotal contribution to the current cardiovascular experimental work. The United States has traditionally held a leading position in this field, supported by robust biomedical research, advanced technological capabilities and a long-standing history of research in vascular biology and atherosclerosis (1). Conversely, the rapid growth in China's research output is indicative of significant increases in national research expenditure and the growing prominence of cardiovascular disease research and translational biomedical science (16).

In addition to these two top contributors, Japan, Germany, the Netherlands and the United Kingdom also produce significant scholarly output owing to their well-established expertise in molecular medicine, experimental pathology and translational cardiovascular studies. Other contributions by France, Sweden, Australia and Canada also indicate the global nature of the ApoE-deficient mouse research context. In general, these trends point to the further domination of traditional Western research centers and, at the same time, to the growing role of Asian scientific leadership in shaping this sphere.

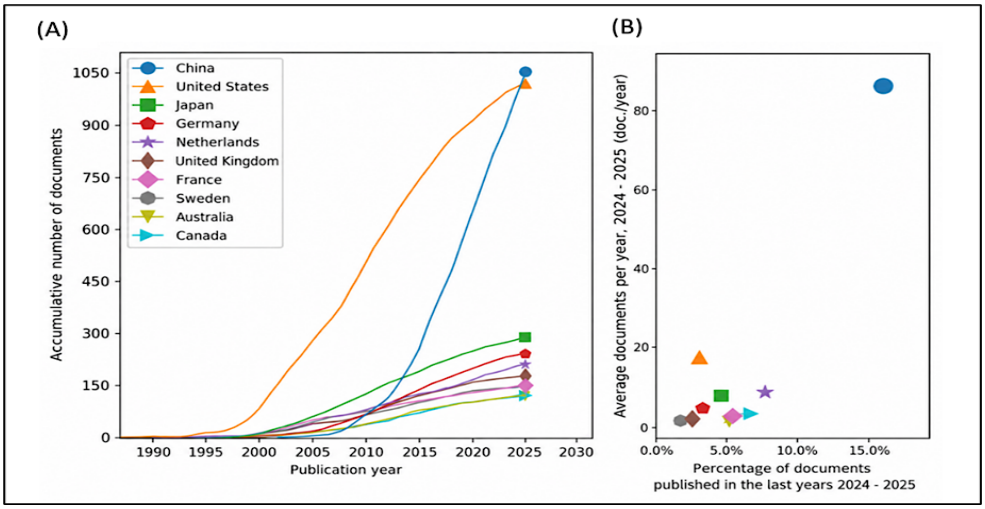

Figure 3: Publication Productivity of the Top 10 Contributing Countries in ApoE-Deficient Mouse Atherosclerosis Research. (A) Cumulative Publication Trends by Country, (B) Percentage Contribution and Average Annual Publication Output During 2024–2025

Top Journals Publishing Research

The top ten journals publishing research on ApoE-deficient mouse models in atherosclerosis are presented in Table 1. The table lists the total number of publications, the publisher name, CiteScore, SCImago Journal Rank (SJR), Source Normalized Impact per Paper (SNIP) and CiteScore Quartile (CQ) for the top 10 journals in ApoE-deficient mouse model research on atherosclerosis.

Table 1: Top 10 Journals by Publication Output in ApoE-deficient Mouse Model Research on Atherosclerosis

Rank	Source Title	Total	Publisher	Cite Score	SJR	SNIP	CQ
1	Arteriosclerosis, Thrombosis and Vascular Biology	273	Wolters Kluwer Health	12.9	2.532	1.670	Q1
2	Atherosclerosis	243	Elsevier	9.6	1.762	1.377	Q1
3	Plos One	135	Public Library of Science	5.4	0.803	1.065	Q2
4	Circulation	119	Wolters Kluwer Health	45.1	8.668	8.297	Q1
5	Biochemical and Biophysical Research Communications	69	Elsevier	4.9	0.748	0.555	Q4
6	Scientific Reports	59	Springer Nature	6.7	0.874	1.213	Q1
7	Journal of Lipid Research	49	American Society for Biochemistry and Molecular Biology Inc.	7.9	1.660	1.202	Q2
8	Circulation Research	47	Wolters Kluwer Health	24.2	4.897	3.623	Q1
9	Cardiovascular Research	45	Oxford University Press	21.3	3.947	2.657	Q1
10	Journal of Clinical Investigation	45	American Society for Clinical Investigation	19.6	4.721	2.174	Q1

The top ten journals that have published studies on ApoE-deficient mouse models in atherosclerosis are primarily high-impact cardiovascular journals, as shown in Table 1. The two most significant sources of publications are Arteriosclerosis, Thrombosis and Vascular Biology (n = 273) and Atherosclerosis (n = 243), which together account for a significant percentage of total research output. This trend reflects that the field is firmly rooted in specialized journals in vascular disease.

Interestingly, eight of the top 10 journals fall within the first quartile (Q1), including Circulation, Circulation Research, Cardiovascular Research and the Journal of Clinical Investigation. Such distribution indicates the strong academic influence of studies in this area, as evidenced by high citation metrics. Notably, Circulation demonstrates the highest CiteScore (CiteScore 45.1; SJR 8.668; SNIP 8.297), followed by Circulation Research (CiteScore 24.2; SJR 4.897; SNIP 3.623), highlighting the substantial scientific visibility of research published in these journals.

Concerning publisher distribution, Wolters Kluwer Health and Elsevier are the dominant players in the publication landscape, underscoring the key role these organizations play in publishing cardiovascular research. While multidisciplinary journals such as PLOS One and Scientific Reports also contribute to broader dissemination, the overall publication pattern indicates that research on ApoE-based atherosclerosis is still primarily published in major cardiovascular and molecular biology journals. This trend highlights the relevance of this model in the mechanistic and translational cardiovascular studies.

Highly Cited Papers

The highly cited publications highlight key research directions that have been investigated using the ApoE-deficient mouse model. Table 2 lists the 10 most-cited articles on ApoE-deficient mouse models of atherosclerosis, highlighting the pioneering studies that have shaped this field. It was shown that the most highly cited publication is the foundational work titled “Severe Hypercholesterolemia and Atherosclerosis in Apolipoprotein E–Deficient Mice Created by Homologous Recombination in ES Cells” by other researcher, which has been cited 2,132 times (5). This foundational work has established ApoE-deficient mice as a powerful genetic model that exhibits spontaneous hypercholesterolemia and

atherosclerotic lesion formation despite a normal diet. The study provided a fundamental experimental platform that enabled further mechanistic studies of atherosclerosis.

Table 2: Top 10 Most Frequently Cited Publications in Research on ApoE-deficient Mouse Model Research in Atherosclerosis

Rank	Title	Citations	Contributions
1	Severe hypercholesterolemia and atherosclerosis in apolipoprotein-e-deficient mice created by homologous recombination in Es cells	2132	This study produced ApoE-deficient mice via targeted homologous recombination in embryonic stem cells and showed that ApoE deficiency alone causes severe hypercholesterolemia and spontaneous atherosclerosis on a normal diet. The results directly identified a genetic relationship between defective lipoprotein clearance and the formation of atherosclerotic lesions. They provided the first robust and reproducible animal model that closely mimics key pathological features of human atherosclerosis.
2	Decreased lesion formation in ccr2-/- mice reveals a role for chemokines in the initiation of atherosclerosis	1915	This study shows that genetic deletion of the chemokine receptor CCR2 markedly reduces atherosclerotic lesion development in ApoE-deficient mice without affecting plasma lipid levels. The results presented herein constitute causal evidence that monocyte recruitment is facilitated by monocyte chemoattractant protein 1 in the development of atherogenesis. These findings confirmed that an inflammatory process, regardless of variations in cholesterol levels, is vital in the initial formation of atherosclerotic lesions.
3	Apoe-deficient mice develop lesions of all phases of atherosclerosis throughout the arterial tree	1687	This study provides the first detailed histopathological description of atherosclerosis in ApoE-deficient mice, indicating that the model develops a full range of human-like lesions, from early monocyte adhesion and foam cell deposition to advanced fibrous plaques with necrotic cores throughout the arterial tree. This study introduced the ApoE-deficient mouse as a reproducible and translational model of progressive atherogenesis, providing an experimental basis for subsequent mechanistic, genetic and therapeutic studies that have significantly advanced the current understanding of cardiovascular biology.
4	Angiotensin II promotes atherosclerotic lesions and aneurysms in apolipoprotein E-deficient mice	1267	This study has clearly shown that chronic angiotensin II infusion significantly accelerates atherosclerotic lesion formation and the development of an abdominal aortic aneurysm in ApoE-deficient mice, without altering blood pressure or plasma lipid levels. This report presented direct experimental data showing that angiotensin II has powerful proinflammatory and proatherogenic effects by increasing macrophage and lymphocyte recruitment and medial remodeling, thereby making the renin-angiotensin system a key mediator of vascular pathology in addition to its hemodynamic function. Moreover, this study provided an experimental model in which angiotensin II induces aneurysm formation in hyperlipidemic mice, a model that has since been adopted as a standard for studying the molecular pathways underlying the association among inflammation, atherosclerosis and aneurysm formation.
5	Adiponectin reduces atherosclerosis in apoliporotein e deficient mice	988	This study shows that adenovirus-induced increases in plasma adiponectin levels are highly effective in reducing atherosclerotic lesion formation in ApoE-deficient mice, regardless of changes in plasma cholesterol, glucose, or insulin levels. This paper was the first to demonstrate in vivo that adiponectin has direct anti-atherogenic effects, inhibiting endothelial cell activation and macrophage foam cell formation, as indicated by reduced expression of vascular cell adhesion molecule-1 and class A scavenger receptor in aortic tissue. In addition, this study identified adiponectin as a protective adipokine linking adipose tissue biology

			to vascular inflammation, thereby extending the hypothesis that metabolic dysregulation plays a mechanistic role in atherosclerosis.
6	Lack of Toll-like receptor 4 or myeloid differentiation factor 88 reduces atherosclerosis and alters plaque phenotype in mice deficient in apolipoprotein E	964	This study has shown that genetic deficiency of Toll-like receptor 4 or its downstream signaling molecule, myeloid differentiation factor 88, significantly inhibits the progression of atherosclerotic lesions in ApoE-deficient mice despite continued hypercholesterolemia. This study presented direct in vivo data demonstrating that innate immune signaling, independent of plasma lipid levels, is a key driver of atherogenesis, resulting in significant reductions in plaque size, lipid deposition, macrophage infiltration and cyclooxygenase-2 expression. Moreover, this study has determined that interference with the TLR4-MyD88 signaling reduces systemic proinflammatory cytokines, such as interleukin-12 and monocyte chemoattractant protein-1 and inhibits endothelial leukocyte adhesion to minimally modified low-density lipoprotein. Taken together, this work has established innate immune mechanisms as major mechanistic intermediates linking hyperlipidemia to vascular inflammation. It has established the basis of targeting Toll-like receptor signaling as a therapeutic approach in atherosclerosis.
7	Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E	951	This study has established that active atherosclerosis is promoted by circulating activated platelets in the ApoE-deficient mice through the stimulationof monocyte recruitment to the arterial wall. Stimulated platelets selectively bound to monocytes via P-selectin- dependent interactions and released proinflammatory chemokines, such as RANTES and platelet factor 4, onto monocytes and the endothelium of the vascular system. The transfer of this chemokine enhanced monocyte integrin activation, adhesion to VCAM-1 on activated endothelium and leukocyte retention in atherosclerotic lesions. Recurrent infusion of activated wild-type platelets greatly increased lesion size but did not affect plasma cholesterol, thereby demonstrating that platelet-mediated inflammatory signaling, independent of lipid effects, promotes atherogenesis.
8	Synthetic LXR ligand inhibits the development of atherosclerosis in mice	943	This study has revealed that chronic stimulation of the liver X receptors with the synthetic agonist GW3965 greatly inhibits the formation of atherosclerotic lesions in LDL receptor-deficient and ApoE-deficient mice. The results indicated that lesion reduction was evident even as plasma cholesterol was minimally altered and, in some instances, triglycerides increased, suggesting that the antiatherogenic effect was not purely lipid-dependent. The study also found that LXR stimulation upregulates cholesterol efflux transporter proteins, including ABCA1 and ABCG1, in macrophages and aortic tissue, providing direct in vivo support for the hypothesis that stimulation of reverse cholesterol transport prevents atherosclerosis.
9	Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis	871	This study shows that chronic overexpression of globular adiponectin can prevent both type 2 diabetes and atherosclerosis in vivo. Adiponectin enhanced insulin sensitivity, increased fat oxidation in skeletal muscle, decreased tissue triglyceride levels and pancreatic β-cell function under conditions of ongoing obesity in ob/ob mice. Globular adiponectin significantly decreased atherosclerotic lesion development in ApoE-deficient mice, with no impact on plasma lipid levels, providing direct evidence that its anti-atherogenic action is mediated by the inhibition of macrophage lipid uptake and vascular inflammation, including scavenger receptor A and tumor necrosis factor alpha. This research thus identified adiponectin as an essential metabolic and vascular protective factor

			linking insulin resistance and atherosclerosis.
10	IFN-gamma potentiates atherosclerosis in apoE knock-out mice	833	This study has shown that impairment of interferon gamma signaling significantly reduces the development of atherosclerotic lesions in mice lacking apolipoprotein E, implying that this cytokine is one of the factors that lead to atherogenesis. Mice deficient in the interferon gamma receptor had much smaller and more lipid-filled plaques containing more collagen, suggesting a transition to a more stable plaque phenotype. In addition to causing local proinflammatory effects in the arterial wall, the lack of interferon gamma signaling also affected systemic lipid metabolism, elevating circulating apolipoprotein A-IV levels. Taken together, this body of work has defined interferon gamma as a key mediator linking adaptive immune stimulation to both plaque formation and destabilization in atherosclerosis.

The second most-cited article, with 1915 citations, "Decreased lesion formation in CCR2-/-mice reveals a role for chemokines in the initiation of atherosclerosis," showed that deletion of CCR2 significantly suppressed lesion formation without affecting plasma lipids (17). This study was the first to provide compelling genetic evidence that inflammatory monocyte recruitment is critical in the initial stages of atherogenesis. Immediately behind this, the third on the list, "Apoe-Deficient Mice Develop Lesions of All Phases of Atherosclerosis Throughout the Arterial Tree," with 1687 citations, provided the first detailed histopathological description of the progression of lesions throughout the arterial tree, thus validating the applicability of the ApoE-deficient mouse model to human atherosclerosis (6).

Other widely cited studies also contributed to the mechanistic explanation of the disease. For example, the number-four study (1,267 citations) revealed that angiotensin II accelerates atherosclerosis and promotes the development of abdominal aortic aneurysms regardless of changes in plasma lipid levels (18). This observation underscored the role of the renin angiotensin system as a major inflammatory pathway in vascular disease. Interestingly, among the 10 most-cited articles on ApoE-deficient mouse atherosclerosis, two studies on adiponectin, with 988 and 871 citations, respectively, reported its protective effects against atherosclerosis in the ApoE-deficient mouse model (19, 20). Other influential studies highlighted the roles of innate immune signaling via the TLR4-MyD88 pathway (964 citations) (21), platelet-mediated inflammatory amplification (951 citations) (22) and the stimulation of anti-atherogenic effects through activation of the liver X receptor (943 citations) (23), Besides, the 10th-ranked article (833 citations) found that interferon gamma was a significant mediator of adaptive immune responses and plaque progression and instability (24).

Collectively, these top-cited articles highlight three key mechanistic themes that have guided research on atherosclerosis in ApoE-deficient mice. To begin with, initial research provided genetic confirmation that the ApoE-deficient model is a lipid-based model of atherogenesis. Second, later studies showed that immune and inflammatory signaling are essential for lesion progression, often independent of cholesterol levels (25). Third, subsequent research examined treatment modalities targeting lipid metabolism, immunology and vascular inflammation. The clustering of citations in these landmark publications underscores their lasting impact on the field's conceptualization and on the direction of experimental studies on ApoE-deficient mice in CVD.

Key Research Themes and Emerging Trends

To better understand the conceptual framework and emergent research themes, a keyword co-occurrence network analysis was conducted. Figure 4 shows the keyword co-occurrence network used by the authors in research on ApoE-deficient mouse models of atherosclerosis. A minimum threshold of 15 occurrences was set and accordingly, 65 keywords met this criterion. Subsequently, eight clusters were formed based on the co-occurrence patterns of the authors' keywords. These clusters encompass cardiometabolic diseases, macrophage-driven lipid metabolism, vascular remodeling, oxidative stress, plaque

stability, immune regulation, microbiome interactions and therapeutic intervention strategies.

Cluster 1 (green) is mainly focused on the central theme of atherosclerosis, with the most predominant keywords being atherosclerosis, mouse, atherogenesis, diabetes, obesity and hypercholesterolemia. This cluster underscores the pivotal role of the ApoE-deficient mouse model as a core experimental platform for the development and progression of cardiometabolic disease. The high likelihood of words related to metabolic disorders appearing indicates that numerous studies in this group use ApoE-deficient mice to investigate the role of metabolic risk factors in vascular pathology. The high connectivity and node size of this cluster indicate that occurrence and link strength are high, suggesting that a significant portion of mechanistic studies is concentrated in this research network. The existence of comorbid conditions, including diabetes and obesity, further indicates that recent research has started to study atherosclerosis in the context of systemic metabolic dysfunction more thoroughly. In general, the cluster indicates a shift in ApoE mouse research, which was previously dominated by early descriptive studies on lesion formation, toward more holistic research that examines the multifaceted interactions among lipid metabolism, metabolic disease and vascular disease.

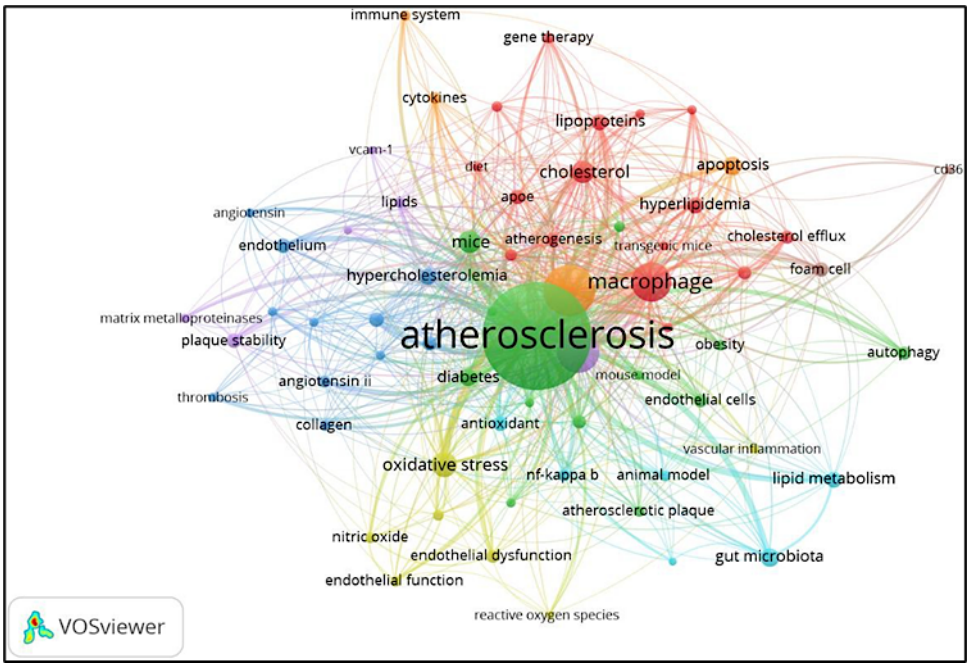

Figure 4: Author's Keyword Co-occurrence Network

Cluster 2 (red) focuses more on the macrophage-mediated pathway in atherosclerosis; the major keywords in this cluster are macrophage, cholesterol, lipoproteins, hyperlipidemia, apoptosis and foam cell. This cluster indicates a high level of research interest in the immunometabolic processes that mediate plaque formation. The prevalence of terms associated with macrophages indicates that much of the literature examines how lipid accumulation in immune cells can lead to the formation of atherosclerotic lesions. The direct connection between macrophages and cholesterol metabolism suggests that lipid handling plays a key role in activating inflammatory responses and in the formation of foam cells, as highlighted in the literature. Moreover, the use of terms such as apoptosis indicates a significant focus on cell death pathways that contribute to plaque instability and the formation of necrotic cores. This cluster underscores the fundamental role of macrophage-mediated lipid metabolism in atherosclerosis research. It suggests that future studies focus more on macrophage heterogeneity, metabolic reprogramming and immunomodulatory strategies targeting cardiovascular disease.

Cluster 3 (blue) is mainly focused on vascular structural regulation and hormonal signaling, with the leading keywords of endothelium, angiotensin, angiotensin II, thrombosis and collagen. The cluster indicates extensive research attention to vascular remodeling processes and the role of the

renin-angiotensin system in driving atherosclerotic disease in the ApoE mouse model. The extracellular matrix–related terms, including collagen, indicate that numerous studies examine arterial wall integrity and the structural modifications associated with plaque formation. Furthermore, the common link in the angiotensin signaling pathway highlights growing interest in the roles of vascular stress and hormonal pathways in endothelial injury and thrombosis. In general, this cluster underscores the importance of vascular stress signaling and structural remodeling in the development of atherosclerosis.

Cluster 4 (yellow) primarily focuses on mechanisms of oxidative stress, with the most common keywords being oxidative stress, nitric oxide, reactive oxygen species, endothelial dysfunction and endothelial function. This cluster indicates that significant attention is paid to redox imbalance as an important mediating factor between vascular injury and metabolic disturbances. The consistent linkage between endothelial dysfunction and oxidative stress indicates that endothelial damage is widely recognized as an initial event in the development of atherosclerotic plaque. Altogether, this cluster underscores the significance of redox signaling in vascular pathology and suggests that mechanisms of oxidative stress-driven endothelial damage remain a focus of research.

Cluster 5 (purple) is primarily focused on plaque stability, with major keywords including plaque stability, matrix metalloproteinases and extracellular matrix-related terms. This group shows a strong interest in the structural remodeling mechanisms governing the integrity of fibrous caps and lesion susceptibility. The prevalence of matrix metalloproteins suggests that numerous studies focus on how extracellular matrix degradation contributes to instability and a predisposition to plaque rupture. Generally, this cluster demonstrates increased interest in studying plaque composition and mechanical stability, with translational significance for preventing plaque rupture and thrombotic complications.

Cluster 6 (orange) is mainly focused on immune regulation in atherosclerosis, with keywords including immune system, cytokines and inflammatory mediators. This cluster indicates a high degree of attention to systemic immune signaling, not limited to macrophage-specific mechanisms. The frequent use of terms related to immunity suggests that numerous studies examine the roles of the innate and adaptive immune systems in plaque development. In general, this cluster demonstrates increased interest in immune cell interactions and inflammatory mediators in atherogenesis, as well as the relevance of immunological processes in the development and progression of atherosclerotic disease.

Cluster 7 (cyan) is mostly related to lipid metabolism and gut microbiota, with the key words being lipid metabolism and gut microbiota. The cluster indicates a new area of research interest in the interactions between hosts and microbes and in their roles in lipid regulation and vascular inflammation. The use of microbiota-related terms indicates that current research is expanding our understanding of how the microbiome influences metabolic disruption and atherosclerotic development. Overall, this cluster shows an increasing systems-level view of atherosclerosis research, with a particular focus on how microbiome-metabolite interactions might contribute to CVD.

Cluster 8 revolves mainly around therapeutic and mechanistic interventions, with the most frequent keywords being gene therapy, atorvastatin, bone marrow transplantation and autophagy. This cluster indicates a research interest in in vivo approaches to regulating atherosclerosis progression in the ApoE-deficient mouse model. The presence of terms such as pharmacological, genetic and cellular interventions indicates that numerous studies are examining the possibility of therapeutic interventions targeting inflammatory and metabolic pathways. In general, this cluster indicates that the ApoE mouse studies have taken a translational turn, focusing on pharmacological targeting, genetic manipulation and cell-based approaches to treating atherosclerosis.

Discussion

The findings of the current bibliometric synthesis demonstrate that research using ApoE-deficient mouse models has evolved from a specialized niche into a mature, multidisciplinary scientific field. The consistent trends in publications over the past 10 years provide evidence that the model is recognized globally as a solid experimental platform for studying cardiovascular disease. This

synthesis is supported by the previous studies, which demonstrated the well-established value of the model in experimental research (26, 27).

The ApoE-deficient mouse model has been widely used due to its high phenotypic relevance. The model can recapitulate the major pathological hallmarks of human atherosclerosis, including systemic hypercholesterolemia, macrophage infiltration and atherosclerotic plaque growth (28-31). The aforementioned features make the ApoE-deficient mouse a useful tool for studying molecular and cellular processes underlying vascular disease. The continued relevance and growth of ApoE-deficient mouse models in experimental cardiovascular research likely can be attributed to these features. Therefore, the model remains a pillar in experimental cardiovascular studies.

The geographic distribution of research output offers a valuable perspective on the dynamic landscape of cardiovascular science. The United States has been a leader in this area for several years, backed by robust knowledge in vascular biology and a rich biomedical research industry (1). It has, however, gradually become less centralized in the research landscape. China has rapidly expanded its research capacity and has progressed from a relatively minor contributor to one of the leading producers of scientific output in this area (32-34). Chinese publication volumes are now equivalent to those of the United States. The increasing research output in China is closely associated with heavy national-level investment in scientific infrastructure and the growing focus on the escalating burden of cardiovascular and cardiometabolic diseases (35-37). Consequently, the two countries are currently making significant contributions to scientific output (38). This trend demonstrates that the field is moving towards a more cooperative and competitive phase, in which leadership in experimental cardiovascular research is becoming more distributed across regions.

The clustering of publications in specialized cardiovascular journals such as Arteriosclerosis, Thrombosis and Vascular Biology and Atherosclerosis suggests that research on ApoE-deficient mice remains tightly coupled to mechanistic and translational cardiovascular science. This is comparable to other bibliometric studies on atherosclerosis research (39, 40). One of the studies found that Arteriosclerosis, Thrombosis and Vascular Biology published the highest number of articles related to T cells and atherosclerosis, followed by Atherosclerosis, PLOS One and Circulation (39). The study also reported that most of the top journals in the field are high-impact Q1 journals, indicating high scientific interest in the mechanistic and translational studies of atherosclerosis. These findings are consistent with the current study, in which publication output was dominated by specialized cardiovascular journals and the majority of the top journals fell into the first quartile.

Citation analysis of the present finding demonstrates that the intellectual foundation of this field remains anchored in several landmark studies that established the relationships among lipid metabolism, inflammatory signaling and immune regulation in atherosclerosis. This is supported by the previous studies demonstrating that lipid, inflammation and immune regulation are interconnected (41-44). These studies were foundational to the molecular understanding that has guided decades of experimental and therapeutic research. Despite the emergence of new research themes, these landmark publications remain important reference points that define current mechanistic research in vascular biology.

Interestingly, the thematic clusters obtained by the keyword analysis are consistent with the mechanistic focus of the most highly cited publications. Numerous studies have highlighted lipid metabolism, inflammatory signaling, immune dysfunction and vascular dysfunction as hallmarks of atherosclerosis. These concepts continue to appear as dominant themes within the keyword network identified in the present study. Consistent with this, inflammatory and immune mechanisms, as well as cytokine-related pathways, emerged as primary research hotspots in previous bibliometric analyses of atherosclerosis research (39). This consistency suggests that new fields such as systems biology, microbiome interactions and precision therapeutics continue to build upon foundational discoveries while simultaneously shaping future research priorities.

The thematic structure identified through keyword analysis in this study suggests that the field is entering a significant phase of development. Lipid metabolism was widely

studied early on. Nevertheless, the recent literature is increasingly integrative and broader in scope, covering immune regulation, microbiome interactions and systems biology. These developments show that contemporary research is shifting away from the classic lipid-based mechanisms. This thematic expansion is also reflected in recent experiments involving ApoE-deficient mice and atherosclerosis, which have increasingly focused on new areas such as endothelial-to-mesenchymal transition (EndMT), molecular docking-assisted therapeutic discovery, modulation of signaling networks and other systems-oriented methods beyond lipid metabolism and inflammation (45-48).

These examples illustrate recent trends that go beyond the typical historical themes that emerged in the network of citations. This shift has coincided with an increasing understanding of atherosclerosis as a multifactorial disease with interconnected molecular, cellular and systemic pathways. Interdisciplinary approaches are thus gaining importance for understanding vascular disease and discovering new therapeutic targets.

In general, this bibliometric analysis provides an in-depth overview of the atherosclerosis research landscape in the ApoE-deficient mouse model. The results show that it is a field with high scientific productivity, extensive international involvement and ongoing relevance to research. The analysis further reveals that a large proportion of studies are published in major cardiovascular journals, underscoring the relevance of this model within the biomedical research community. However, the field continues to evolve. The thematic patterns identified in this study suggest an expansion toward a broader and more integrated biological perspective. Emerging research areas such as gut microbiome interactions, autophagy pathways and precision therapeutic interventions indicate that recent studies increasingly explore complex mechanisms beyond traditional lipid-focused pathways.

This study has several practical implications. The list of landmark publications and thematic clusters identified will be useful to researchers entering the field, providing an overview of core concepts and topics in current research. This information can be used by funding agencies and policymakers to prioritize novel areas of strategic importance, such as immunometabolism, microbiome-host interactions and targeted therapeutic interventions. Beyond that, the growing interest in multidisciplinary approaches suggests that future studies should integrate molecular biology, bioinformatics, systems biology and translational medicine to investigate the complex mechanisms of atherosclerosis. These joint efforts can help accelerate the development of new preventive and therapeutic tools against cardiovascular disease.

Conclusion

This bibliometric study provides a comprehensive overview of the global research landscape surrounding ApoE-deficient mouse models in atherosclerosis. The analysis reveals sustained scientific productivity, broad international research participation and a strong concentration of publications within leading cardiovascular journals.

This study highlights the role of ApoE-deficient mice as a key experimental model in atherosclerosis research. The ApoE-deficient mouse acts as a foundational experimental model for investigating the interconnected roles of lipid metabolism, vascular inflammation and immune regulation in atherosclerosis. The thematic patterns identified through keyword analysis also demonstrate a growing research interest in emerging areas such as microbiome interactions, autophagy pathways and targeted therapeutic interventions.

Despite the above analysis, this study has several limitations. First, in the search strategy, the specific symbol "ApoE^{-}/$^{-}$" was not directly identified; instead, more general textual terms such as "apolipoprotein E" and "ApoE knockout" were used, which likely ensured that most of the identified studies were located. However, studies that use only symbolic notation without textual descriptors may have been underrepresented. Moreover, our search was limited to the title field to enhance precision during retrieval, which might have decreased sensitivity by omitting relevant studies that used the model in the abstract or author keywords but not in the title.

In addition, only publications indexed in Scopus and Web of Science were analyzed and only original research articles in English were included. Although these requirements reduced the dataset's inconsistency and unreliability, they might have omitted related studies published in

other databases and languages, as well as other document types, such as reviews and conference papers. Citation-based indicators for the most recent years should also be interpreted with caution, as newly published studies may not yet be fully indexed or have accumulated sufficient citations. Lastly, the co-occurrence analysis relied on the authors' keywords and a predetermined occurrence threshold, which may have led to the underrepresentation of emerging or low-frequency research themes.

Future research is suggested to be conducted using several databases with a wider range of search strings. Further studies could explore more detailed bibliometric analysis and evaluations of more recent publications, as this mouse model continues to evolve.

Abbreviations

ApoE: Apolipoprotein E, CQ: CiteScore Quartile, CVD: Cardiovascular Disease, Q1: First Quartile, SJR: SCImago Journal Rank, SNIP: Source Normalized Impact per Paper.

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Author Contributions

Fauziah Md Tahib: Conceptualization, Methodology, Formal Analysis, Writing-Original Draft, Siti Norashikin Mohd Tambeh: Conceptualization, Writing-Review, Editing, Supervision, Awla Mohd Azraai: Conceptualization, Writing-Review, Editing, Supervision, Nasibah Azme: Conceptualization, Methodology, Formal Analysis, Writing-Original Draft, Funding Acquisition, Supervision.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability

The data generated in this study are available from the corresponding author upon reasonable request.

Declaration of Artificial Intelligence (AI) Assistance

Artificial intelligence (AI) tools were used solely to assist with language refinement and manuscript clarity. ChatGPT (OpenAI) and Grammarly were utilized to enhance sentence structure, grammar and readability. All study design, data collection, analysis, interpretation and scientific conclusions were performed independently by the authors. The authors take full responsibility for the content's originality, interpretation and accuracy.

Ethics Approval

This study did not involve human participants or animals; therefore, ethical approval was not required.

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References

1. Libby P. The changing landscape of atherosclerosis. Nature. 2021;592(7855):524–33. doi: 10.1038/s41586-021-03392-8
2. Moore KJ, Sheedy FJ, Fisher EA. Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol. 2013;13(10):709–21. doi: 10.1038/nri3520
3. Tang WH, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. Circ Res. 2017;120(7):1183–96. doi: 10.1161/CIRCRESAHA.117.309715
4. Getz GS, Reardon CA. Animal models of atherosclerosis. Arterioscler Thromb Vasc Biol. 2012;32(5):1104–15. doi: 10.1161/ATVBAHA.111.237693
5. Plump AS, Smith JD, Hayek T, *et al*. Severe hypercholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells. Cell. 1992;71(2):343–53. doi: 10.1016/0092-8674(92)90362-g
6. Nakashima Y, Plump AS, Raines EW, *et al*. ApoE-deficient mice develop lesions of all phases of atherosclerosis throughout the arterial tree. Arterioscler Thromb. 1994;14(1):133–40. doi: 10.1161/01.atv.14.1.133
7. Vasquez EC, Peotta VA, Gava AL, *et al*. Cardiac and vascular phenotypes in the apolipoprotein E-deficient mouse. J Biomed Sci. 2012;19(1):22. doi: 10.1186/1423-0127-19-22
8. Lo Sasso G, Schlage WK, Boué S, *et al*. The Apoe(-/-) mouse model: a suitable model to study cardiovascular and respiratory diseases in the context of cigarette smoke exposure and harm reduction. J Transl Med. 2016;14(1):146. doi: 10.1186/s12967-016-0901-1
9. Torikai H, Chen MH, Jin L, *et al*. Atherogenesis in Apoe-/- and Ldlr-/- mice with a genetically resistant background. Cells. 2023;12(9):1255. doi: 10.3390/cells12091255
10. Golforoush P, Yellon DM, Davidson SM. Mouse models of atherosclerosis and their suitability for the

study of myocardial infarction. Basic Res Cardiol. 2020;115(6):73.
doi: 10.1007/s00395-020-00829-5
11. Tang WH, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. Circ Res. 2017;120(7):1183–96.
doi: 10.1161/CIRCRESAHA.117.309715
12. Ahmad T, Dhama K, Tiwari R, *et al*. Bibliometric analysis of the top 100 most cited studies in apolipoprotein E (ApoE) research. Narra J. 2021;1(1):e2.
doi:10.52225/narraj.v1i1.2
13. Wang Z, Zhu X, Wen Y, *et al*. Bibliometric analysis of global research on the role of apolipoprotein E in Alzheimer's disease. Heliyon. 2023;9(7):e17987.
doi:10.1016/j.heliyon.2023.e17987
14. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
doi: 10.1136/bmj.n71
15. Donthu N, Kumar S, Mukherjee D, *et al*. How to conduct a bibliometric analysis: an overview and guidelines. J Bus Res. 2021;133:285–96.
doi: 10.1016/j.jbusres.2021.04.070
16. Gao F, Sun RJ, Ji Y, *et al*. Cardiovascular research is thriving in China. Br J Pharmacol. 2015;172(23):5430–5434.
doi: 10.1111/bph.12826
17. Boring L, Gosling J, Cleary M, *et al*. Decreased lesion formation in CCR2-/- mice reveals a role for chemokines in the initiation of atherosclerosis. Nature. 1998;394(6696):894–97.
doi: 10.1038/29788
18. Daugherty A, Manning MW, Cassis LA. Angiotensin II promotes atherosclerotic lesions and aneurysms in apolipoprotein E-deficient mice. J Clin Invest. 2000;105(11):1605–12.
doi: 10.1172/JCI7818
19. Okamoto Y, Kihara S, Ouchi N, *et al*. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation. 2002;106(22):2767–70.
doi:10.1161/01.cir.0000042707.50032.19
20. Yamauchi T, Kamon J, Waki H, *et al*. Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. J Biol Chem. 2003;278(4):2461–68.
doi:10.1074/jbc.M209033200
21. Michelsen KS, Wong MH, Shah PK, *et al*. Lack of Toll-like receptor 4 or myeloid differentiation factor 88 reduces atherosclerosis and alters plaque phenotype in mice deficient in apolipoprotein E. Proc Natl Acad Sci U S A. 2004;101(29):10679–84.
doi:10.1073/pnas.0403249101
22. Huo Y, Schober A, Forlow SB, *et al*. Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E. Nat Med. 2003;9(1):61–7.
doi:10.1038/nm810
23. Joseph SB, McKilligin E, Pei L, *et al*. Synthetic LXR ligand inhibits the development of atherosclerosis in mice. Proc Natl Acad Sci U S A. 2002;99(11):7604–9.
doi:10.1073/pnas.112059299
24. Gupta S, Pablo AM, Jiang XC, *et al*. IFN-γ potentiates atherosclerosis in ApoE knockout mice. J Clin Invest. 1997;99(11):2752–2761.
doi: 10.1172/JCI119465
25. Nowak WN, Deng J, Ruan XZ, *et al*. Reactive oxygen species generation and atherosclerosis. Arterioscler Thromb Vasc Biol. 2017;37(5):e41–52.
doi:10.1161/ATVBAHA.117.309228
26. Meir KS, Leitersdorf E. Atherosclerosis in the apolipoprotein E-deficient mouse: a decade of progress. Arterioscler Thromb Vasc Biol. 2004;24(6):1006–14.
doi: 10.1161/01.ATV.0000128849.12617.f4
27. Jawień J, Nastałek P, Korbut R. Mouse models of experimental atherosclerosis. J Physiol Pharmacol. 2004;55(3):503–17
https://pubmed.ncbi.nlm.nih.gov/15381823/
28. Zhang SH, Reddick RL, Piedrahita JA, *et al*. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein E. Science. 1992;258(5081):468–71.
doi:10.1126/science.1411543
29. Ilyas I, Little PJ, Liu Z, *et al*. Mouse models of atherosclerosis in translational research. Trends Pharmacol Sci. 2022;43(11):920–39.
doi:10.1016/j.tips.2022.06.009
30. Poznyak AV, Silaeva YY, Orekhov AN, *et al*. Animal models of human atherosclerosis: current progress. Braz J Med Biol Res. 2020;53(6):e9557.
doi:10.1590/1414-431x20209557
31. Oppi S, Lüscher TF, Stein S. Mouse models for atherosclerosis research—Which is my line? Front Cardiovasc Med. 2019;6:46.
doi:10.3389/fcvm.2019.00046
32. Pisani N, Boekhout HD, Heemskerk EM, *et al*. China's rise as global scientific powerhouse: a trajectory of international collaboration and specialization in high-impact research. Res Policy. 2025;54(8):105288.
doi:10.1016/j.respol.2025.105288
33. Baker S. China overtakes United States on contribution to research in Nature Index. Nature. 2023.
doi:10.1038/d41586-023-01705-7
34. Damahuri AA, Mohamad M, Rahman THA, *et al*. The heart's fibrous web: A bibliometric analysis of cardiac fibrosis in Asia and Oceania. Medicine (Baltimore). 2026;105(22):e49017.
doi:10.1097/MD.0000000000049017
35. Li X, Zhang Y, Wang M, *et al*. Prevalence and awareness of cardiometabolic risk factors in southern Chinese population with coronary artery disease. Sci World J. 2013;2013:416192.
doi:10.1155/2013/416192
36. Wang ZW. Status of cardiovascular disease in China. J Geriatr Cardiol. 2023;20(6):397–98.
doi:10.26599/1671-5411.2023.06.006
37. Bei Y, Yang T, Xiao J. Cardiovascular medicine in China: what can we do to achieve the Healthy China 2030 plan? BMC Med. 2018;16(1):132.
doi:10.1186/s12916-018-1133-4
38. Zhu J, Liu W. Comparing like with like: China ranks first in SCI-indexed research articles since 2018. Scientometrics. 2020;124(2):1691–1700.
doi:10.1007/s11192-020-03525-2
39. Wei N, Xu Y, Li Y, *et al*. A bibliometric analysis of T cell and atherosclerosis. Front Immunol. 2022;13:948314.
doi:10.3389/fimmu.2022.948314

40. Wang JH, Pan GR, Jiang L. A bibliometric analysis of immunotherapy for atherosclerosis: trends and hotspots prediction. Front Immunol. 2024;15:1493250. doi:10.3389/fimmu.2024.1493250
41. Qian T, Guo D, Sun L, *et al*. Crosstalk between lipid metabolism and macrophages in atherosclerosis: therapeutic potential of natural products. Front Cardiovasc Med. 2025;12:1529924. doi:10.3389/fcvm.2025.1529924
42. Glass CK, Witztum JL. Atherosclerosis: the road ahead. Cell. 2001;104(4):503–16. doi:10.1016/S0092-8674(01)00238-0
43. Pandit R, Yurdagul A. The atherosclerotic plaque microenvironment as a therapeutic target. Curr Atheroscler Rep. 2025;27(1):47. doi:10.1007/s11883-025-01294-y
44. Wang SY, Chen YS, Jin BY, *et al*. The cGAS-STING pathway in atherosclerosis. Front Cardiovasc Med. 2025;12:1550930. doi:10.3389/fcvm.2025.1550930
45. Gao Y, Ye F, Dong Y, *et al*. Salvianic acid A ameliorates atherosclerosis through metabolic-dependent anti-EndMT pathway and repression of TGF-β/ALK5 signaling. Phytomedicine. 2025;136:156307. doi: 10.1016/j.phymed.2024.156307
46. Pu Y, Dong P, He L, *et al*. Endothelial TBK1 deficiency inhibits endothelial-to-mesenchymal transition and atherogenesis through suppressing PAK1/ERK1/2 signaling. Circ Res. 2026;138(6):e326815. doi:10.1161/CIRCRESAHA.125.326815
47. Ma M, Zhong J, Tai Y, *et al*. Combining RNA-seq, molecular docking and experimental verification to explore the mechanism of BAM15 as a potential drug for atherosclerosis. Sci Rep. 2025;15(1):13347. doi:10.1038/s41598-025-98209-3
48. Cheng S, Wang Y, Tong, T, *et al*. Mangiferin attenuates Ang II-induced abdominal aortic aneurysm by blocking Lys591-mediated nuclear translocation of STAT3. Phytomedicine. 2025. doi: 10.1016/j.phymed.2025.157101

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