Carotid Disease Pathophysiology: Systematic Review with ☸SAIMSARA.

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Abstract: The aim of this paper is to systematically review and synthesize the current understanding of carotid disease pathophysiology, integrating diverse findings from recent academic literature to identify key mechanisms, associated risk factors, clinical implications, and future research directions. The review utilises 198 studies with 267483 total participants (naïve ΣN). The standardized prevalence of carotid atherosclerosis (CA) in a middle-aged and older Chinese population was 36.2%. This high prevalence underscores the widespread impact of carotid disease, driven by complex interactions between hemodynamic forces, inflammatory processes, molecular dysregulation, and systemic risk factors. The significant heterogeneity in study designs and reporting, particularly the lack of specified methodologies and comprehensive statistical data in many studies, represents the primary limitation affecting the certainty and generalizability of current findings. Future research should focus on large-scale, longitudinal multi-omics studies to elucidate causal pathways and develop precision medicine approaches for diagnosis and treatment.

Keywords: Carotid artery disease; Atherosclerosis; Pathophysiology; Inflammation; Endothelial dysfunction; Hemodynamics; Vascular remodeling; Carotid stenosis; Biomarkers; Moyamoya disease

Review Stats

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- Scope: All fields
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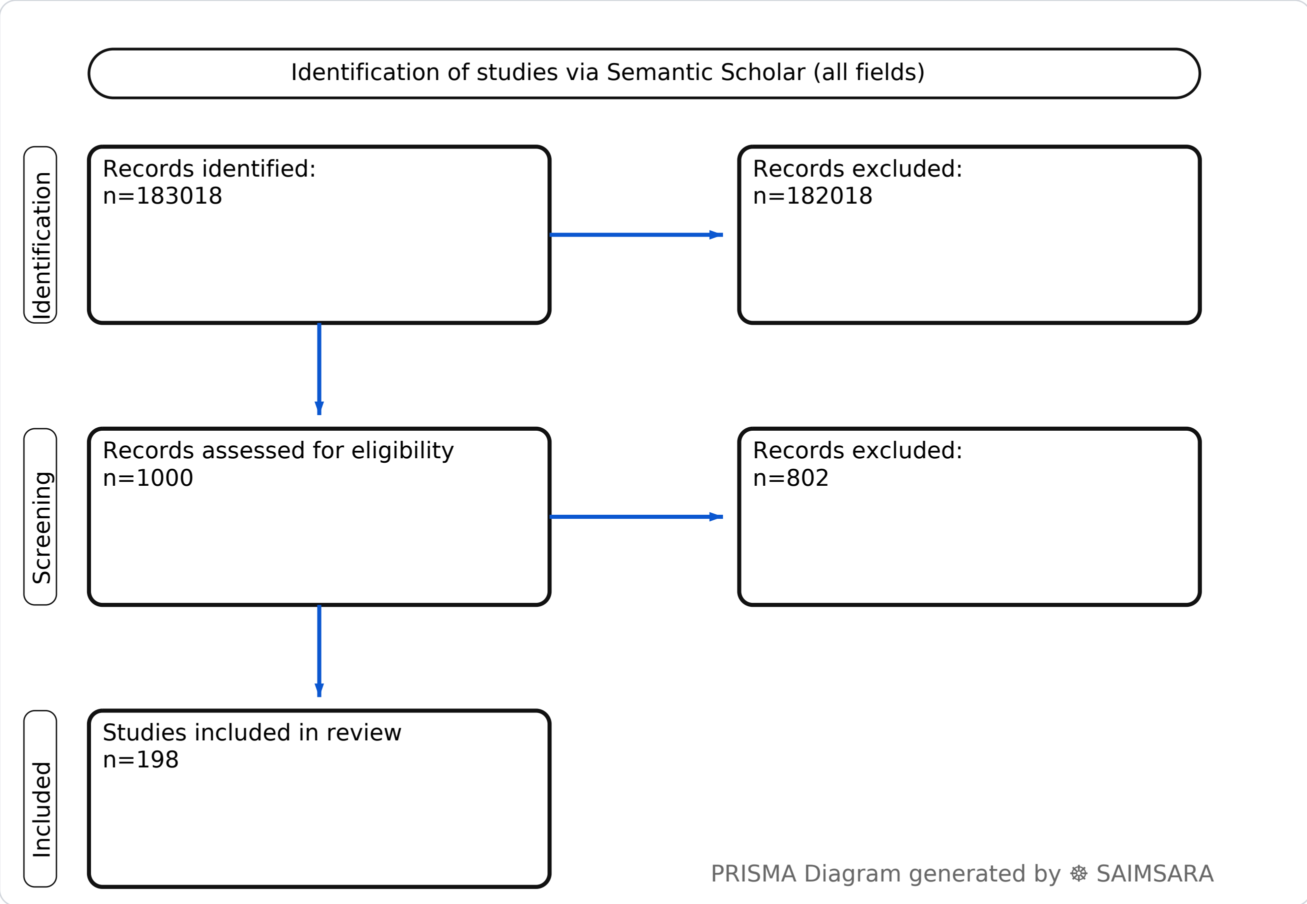
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 198
- Total study participants (naïve ΣN): 267483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Records excluded:
n=182018
Screening
Records assessed for eligibility
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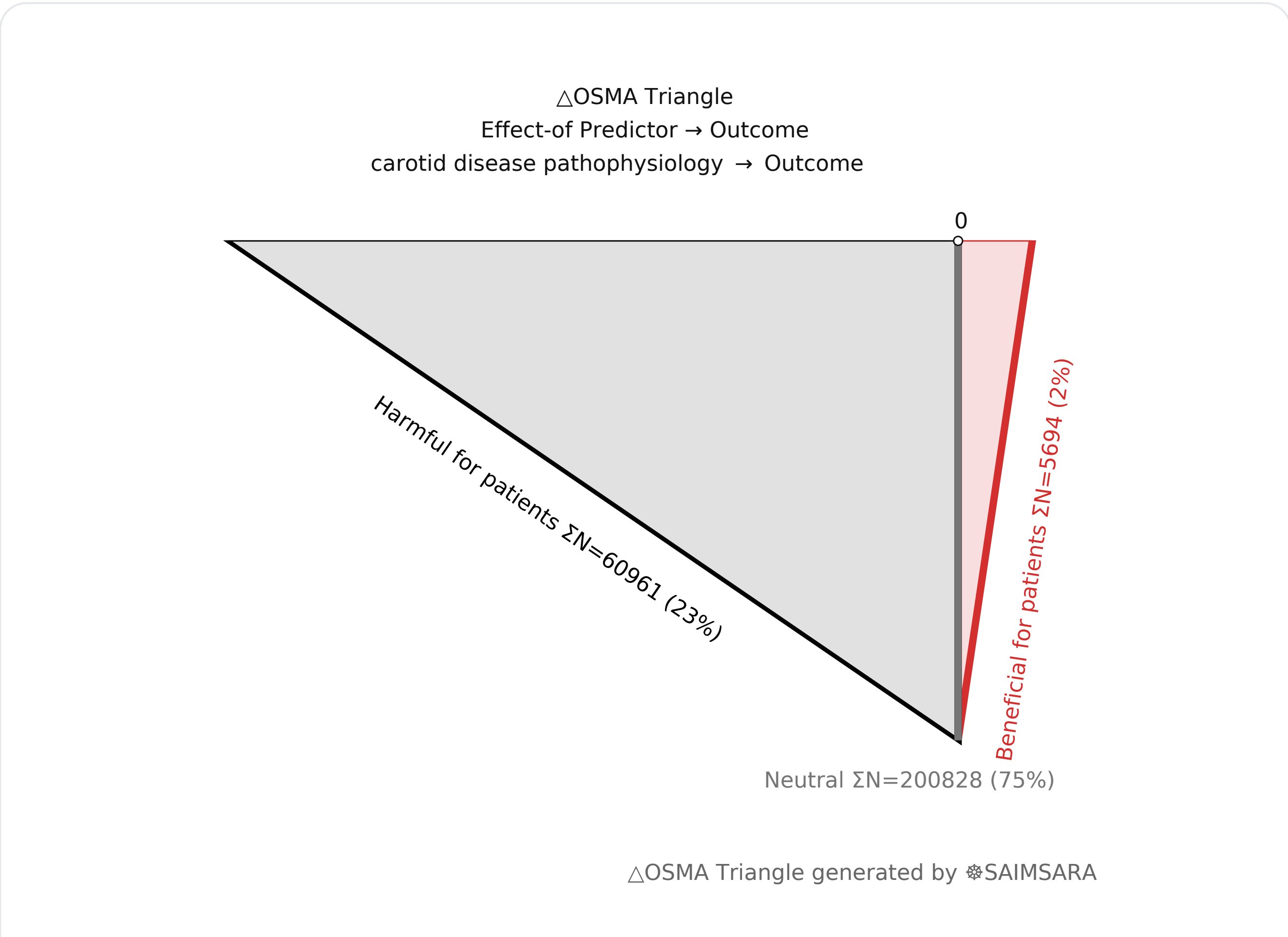
Records excluded:
n=802
Included
Studies included in review
n=198
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
carotid disease pathophysiology → Outcome
0
Harmful for patients ΣN=60961 (23%)
Beneficial for patients ΣN=5694 (2%)
Neutral ΣN=200828 (75%)
△OSMA Triangle generated by ☸SAIMSARA

Outcome-Sentiment Meta-Analysis (OSMA): *(LLM-only)*

Frame: Effect-of Predictor → Outcome • *Source*: Semantic Scholar

Outcome: Outcome Typical timepoints: 12-mo, 4-day. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, occlusion, functional.

Predictor: carotid disease pathophysiology — exposure/predictor. Routes seen: sc. Typical comparator: controls, healthy individuals, less active patients, healthy controls.…

- **1) Beneficial for patients** — Outcome with carotid disease pathophysiology — [61], [74], [79], [90], [93], [95], [99], [100] — ΣN=5694
- **2) Harmful for patients** — Outcome with carotid disease pathophysiology — [2], [15], [51], [52], [56], [57], [58], [59], [60], [66], [67], [68], [69], [70], [71], [72], [73], [75], [76], [77], [82], [83], [85], [86], [89], [92], [94], [97], [98] — ΣN=60961
- **3) No clear effect** — Outcome with carotid disease pathophysiology — [1], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [53], [54], [55], [62], [63], [64], [65], [78], [80], [81], [84], [87], [88], [91], [96], [101], [102], [103], [104], [105], [106], [107], [108], [109], [110], [111], [112], [113], [114], [115], [116], [117], [118], [119], [120], [121], [122], [123], [124], [125], [126], [127], [128], [129], [130], [131], [132], [133], [134], [135], [136], [137], [138], [139], [140], [141], [142], [143], [144], [145], [146], [147], [148], [149], [150], [151], [152], [153], [154], [155], [156], [157], [158], [159], [160], [161], [162], [163], [164], [165], [166], [167], [168], [169], [170], [171], [172], [173], [174], [175], [176], [177], [178], [179], [180], [181], [182], [183], [184], [185], [186], [187], [188], [189], [190], [191], [192], [193], [194], [195], [196], [197], [198] — ΣN=200828

1) Introduction

Carotid artery disease, primarily atherosclerosis, represents a significant global health burden due to its profound implications for cerebrovascular and cardiovascular events. Understanding the intricate pathophysiology of carotid disease is crucial for developing effective diagnostic tools, therapeutic interventions, and preventive strategies. This paper synthesizes current research on the multifaceted mechanisms underlying carotid disease, ranging from initial plaque formation to its systemic and cerebral manifestations.

2) Aim

The aim of this paper is to systematically review and synthesize the current understanding of carotid disease pathophysiology, integrating diverse findings from recent academic literature to identify key mechanisms, associated risk factors, clinical implications, and future research directions.

3) Methods

Systematic review with multilayer AI research agent: keyword normalization, retrieval & structuring, and paper synthesis (see SAIMSARA About section for details).

- **Bias:** The included studies present a wide range of designs, from case reports and cross-sectional studies to prospective cohorts and experimental animal models. Many studies lack explicit reporting of statistical methods, sample size rationale, or follow-up duration, introducing potential biases related to selection, reporting, and generalizability. The qualitative nature of many findings, particularly in case studies and experimental models, limits the ability to draw definitive quantitative conclusions across the entire body of literature.

4) Results

4.1 Study characteristics:

The review encompassed a broad spectrum of study designs, including prospective and retrospective cohorts, cross-sectional analyses, case-control studies, and numerous experimental investigations utilizing animal models (e.g., mice, rats, minipigs, rabbits) and human tissue samples. Patient populations varied widely, from healthy individuals and those with specific risk factors (e.g., diabetes, hypertension, HIV, rheumatoid arthritis) to patients with advanced carotid stenosis, ischemic stroke, or rare conditions like Moyamoya disease and fibromuscular dysplasia. Follow-up periods, when specified, ranged from short-term (e.g., 7 days to 3 months) to long-term (e.g., 5 to 24 years).

4.2 Main numerical result aligned to the query:

The standardized prevalence of carotid atherosclerosis (CA) in a middle-aged and older Chinese population was 36.2% [106].

4.3 Topic synthesis:

- **Atherosclerosis Initiation and Progression:** Carotid atherosclerosis begins with endothelial dysfunction and low-density lipoprotein (LDL) accumulation, progressing to inflammation, foam cell formation, plaque growth, and fibrous cap development [1]. Smooth muscle cells (SMCs) transition to intermediate cell states, differentiating into macrophage-like and fibrochondrocyte-like cells, which are critical for atherosclerosis development [29, 157]. Genetic variations, such as those in the 1p13.3 and 19q13.2 regions, are associated with increased risk of carotid artery disease (CAAD) [115].

- **Hemodynamic and Structural Factors:** Disturbed flow patterns, carotid bifurcation geometry, high wall shear stress (WSS), and low relative residence time (RRT) contribute significantly to plaque instability and rupture risk [1, 19, 69]. Arterial stiffness, measured by pulse wave velocity (PWV) or stiffness index Beta, is associated with increased carotid intima-media thickness (IMT) and is implicated in cardiovascular disease pathophysiology [40, 57, 58, 95, 111, 113, 144]. For instance, patients with hyperuricemia showed higher IMT (0.97 ± 0.22 mm vs 0.91 ± 0.18 mm, $p<0.001$) and stiffness index Beta (8.3 ± 3.2 vs 7.5 ± 2.7, $p=0.005$) compared to controls [111].
- **Inflammation and Immune Mechanisms:** Multi-omics integration identified key molecular signatures related to coagulation, necroptosis, inflammation, and cholesterol metabolism in carotid atherosclerosis [3]. Serum galectin-3 (Gal-3) levels are significantly higher in patients with advanced carotid artery stenosis (CAS) compared to controls [4, 158]. Elevated plasma levels of C16:0 and C24:1 ceramides, correlating with immune activation and inflammation, are associated with carotid artery atherosclerosis progression [15]. Cytomegalovirus (CMV) presence in carotid plaques is significantly higher in patients with bilateral carotid artery stenosis (63%) [23].
- **Molecular and Epigenetic Regulation:** Tobacco smoking is associated with differential DNA methylation at multiple loci in carotid atherosclerotic lesions, supporting a role for epigenetic regulation [22]. Increased methylation of the TP53 promoter is associated with ischemic stroke (IS) and correlates with carotid intima-media thickness (IMT) and atherosclerosis severity [59]. Hyperglycemia upregulates MALAT1 in macrophage-derived exosomes, promoting vascular disease, a mechanism observed in rat carotid artery balloon injury [138].
- **Systemic and Cerebral Connections:** Carotid artery stenosis is linked to various systemic and cerebral manifestations, including ocular ischemia syndrome (OIS) [2, 102], cortical thinning [20], and vascular cognitive impairment (VCI) [48, 67, 125]. Carotid atherosclerosis is associated with plasma amyloid-beta (Aβ) levels and increased brain Aβ burden, suggesting a link to Alzheimer’s disease (AD) pathophysiology [30, 44, 60, 101]. Intracranial artery calcification and carotid stenosis are associated with cerebral small vessel disease markers like white matter hyperintensities (WMHs) and cerebral microbleeds (CMBs) [116, 123].
- **Biomarkers and Risk Factors:** Several circulating biomarkers are implicated in carotid disease pathophysiology, including mean platelet volume (MPV) and monocyte to high-density lipoprotein cholesterol ratio (MHR), which are higher in advanced CAS and predict plaque formation [14, 94]. Orthostatic hypotension (OH) is associated with future cardiovascular disease (CVD) events and subclinical CVD, including carotid intimal thickness and plaque [121]. A high low-/high-density lipoprotein cholesterol ratio (LDL-C/HDL-C) is

associated with an increased risk of carotid plaques [73, 105].

5) Discussion

5.1 Principal finding:

The standardized prevalence of carotid atherosclerosis in a middle-aged and older Chinese population was 36.2% [106], highlighting its significant presence and indicating a widespread subclinical burden of disease.

5.2 Clinical implications:

- **Early Detection:** Routine screening for carotid intima-media thickness (CIMT) and plaque presence, especially in high-risk populations, can aid in early detection of cardiovascular disease risk [54, 82, 98].
- **Biomarker Utility:** Elevated serum galectin-3 (Gal-3) levels [4, 158], mean platelet volume (MPV), and monocyte to high-density lipoprotein cholesterol ratio (MHR) [14, 94] may serve as potential markers for carotid artery stenosis severity and plaque formation, guiding risk stratification.
- **Risk Factor Management:** Intensive medical management of vascular risk factors, including dyslipidemia (e.g., high LDL-C/HDL-C ratio) [73, 105], hypertension, diabetes, and smoking [135], is crucial for preventing carotid plaque development and progression.
- **Therapeutic Targets:** Understanding the role of specific molecular pathways, such as Rho kinase 2 (ROCK2) [56], microRNAs [162], and inflammatory mediators [79], may lead to novel therapeutic interventions for carotid atherosclerosis and its complications.
- **Systemic Disease Link:** Carotid disease often coexists with other systemic conditions like inflammatory bowel disease (IBD) [122] and chronic kidney disease (CKD) [43], necessitating a holistic approach to patient management and risk assessment.

5.3 Research implications / key gaps:

- **Molecular Signature Validation:** Further studies are needed to validate the identified molecular signatures related to coagulation, necroptosis, inflammation, and cholesterol metabolism in larger, diverse cohorts and to assess their predictive value for adverse events and therapeutic response [3].
- **Hemodynamic-Plaque Interaction:** Research should precisely quantify the impact of specific flow disturbances (e.g., high WSS, low RRT) on plaque composition and vulnerability across different carotid artery segments using advanced imaging and computational fluid

dynamics [12, 19, 69, 165].

- **Epigenetic Mechanisms:** The exact role of epigenetic modifications, such as DNA methylation (e.g., TP53 promoter, N6-methyladenine) [22, 59, 152], in carotid atherosclerosis initiation and progression requires further investigation, including longitudinal studies to determine causality.
- **Carotid-Brain Axis:** More research is needed to elucidate the precise mechanisms linking carotid artery stiffness and atherosclerosis to cognitive impairment, dementia, and cerebral small vessel disease, potentially through impaired glymphatic function or altered cerebral hemodynamics [48, 60, 67, 71, 101, 104].
- **Personalized Medicine:** Future studies should investigate how genetic variability (e.g., VEGFA gene SNP [52], PHACTR1 gene variant [142]) and individual differences in immune responses (e.g., myeloid-specific cannabinoid CB1 receptor [155]) influence carotid disease pathophysiology to enable personalized prevention and treatment strategies.

5.4 Limitations:

- **Heterogeneous Study Designs** — The diverse range of study designs, including many without specified methodology, limits the ability to synthesize findings uniformly and draw strong causal inferences.
- **Incomplete Statistical Reporting** — A significant number of studies did not report comprehensive statistical data (e.g., p-values, confidence intervals, sample sizes), hindering quantitative comparisons and meta-analysis.
- **Varied Population Demographics** — The inclusion of diverse populations (human, animal models, specific disease cohorts) and settings limits the generalizability of findings across different ethnic groups and clinical contexts.
- **Qualitative Data Dominance** — Many reported results are qualitative descriptions of associations or observed changes rather than precise quantitative measurements, making it challenging to establish consistent effect sizes.
- **Lack of Longitudinal Data** — A substantial portion of studies are cross-sectional, which precludes the determination of temporal relationships and causality in the progression of carotid disease.

5.5 Future directions:

- **Longitudinal Cohort Studies** — Conduct large-scale, prospective longitudinal studies to track the progression of carotid atherosclerosis and its associated clinical outcomes over extended periods.

- **Multi-Omics Integration** — Integrate multi-omics data (genomics, proteomics, metabolomics) with advanced imaging techniques to build comprehensive models of carotid plaque vulnerability.
- **Therapeutic Target Validation** — Validate novel therapeutic targets identified from molecular and cellular studies in preclinical models and translate promising findings into human clinical trials.
- **Artificial Intelligence Diagnostics** — Develop and validate AI-powered diagnostic tools, such as the Attention-UNet model for plaque segmentation [91], to improve early detection and risk stratification.
- **Personalized Risk Stratification** — Investigate the utility of combining traditional risk factors with novel biomarkers and genetic profiles to create more precise, personalized risk stratification models for carotid disease.

6) Conclusion

The standardized prevalence of carotid atherosclerosis (CA) in a middle-aged and older Chinese population was 36.2% [106]. This high prevalence underscores the widespread impact of carotid disease, driven by complex interactions between hemodynamic forces, inflammatory processes, molecular dysregulation, and systemic risk factors. The significant heterogeneity in study designs and reporting, particularly the lack of specified methodologies and comprehensive statistical data in many studies, represents the primary limitation affecting the certainty and generalizability of current findings. Future research should focus on large-scale, longitudinal multi-omics studies to elucidate causal pathways and develop precision medicine approaches for diagnosis and treatment.

References

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Figure 1. Publication-year distribution of included originals

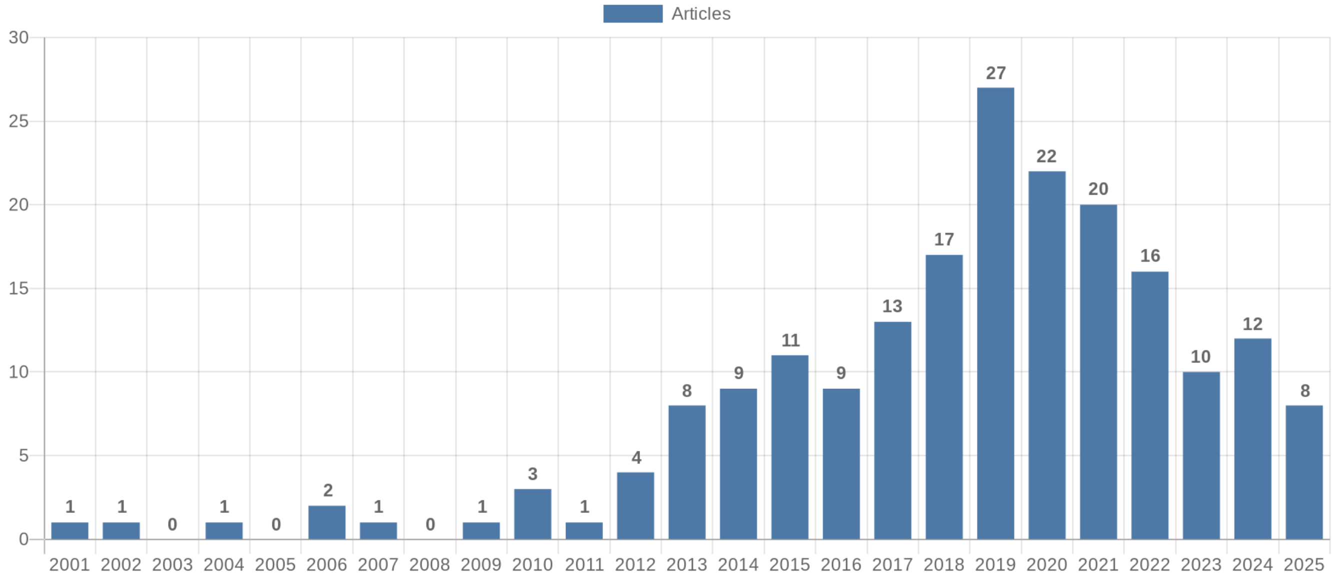

Figure 2. Study-design distribution of included originals

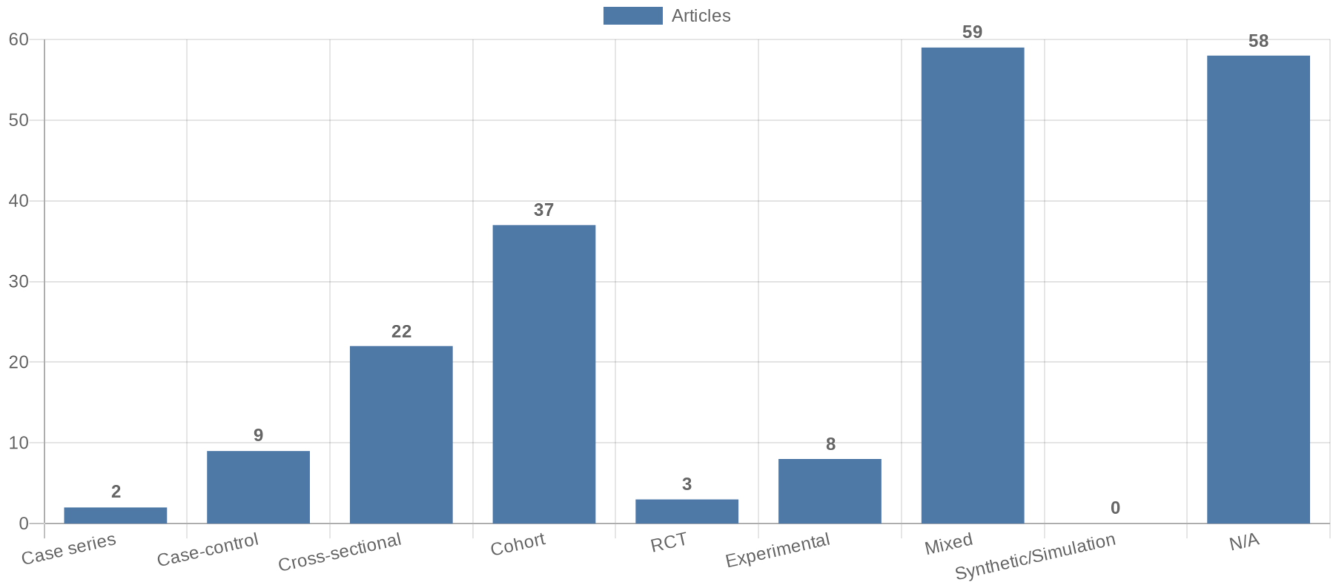

Figure 3. Study-type (directionality) distribution of included originals

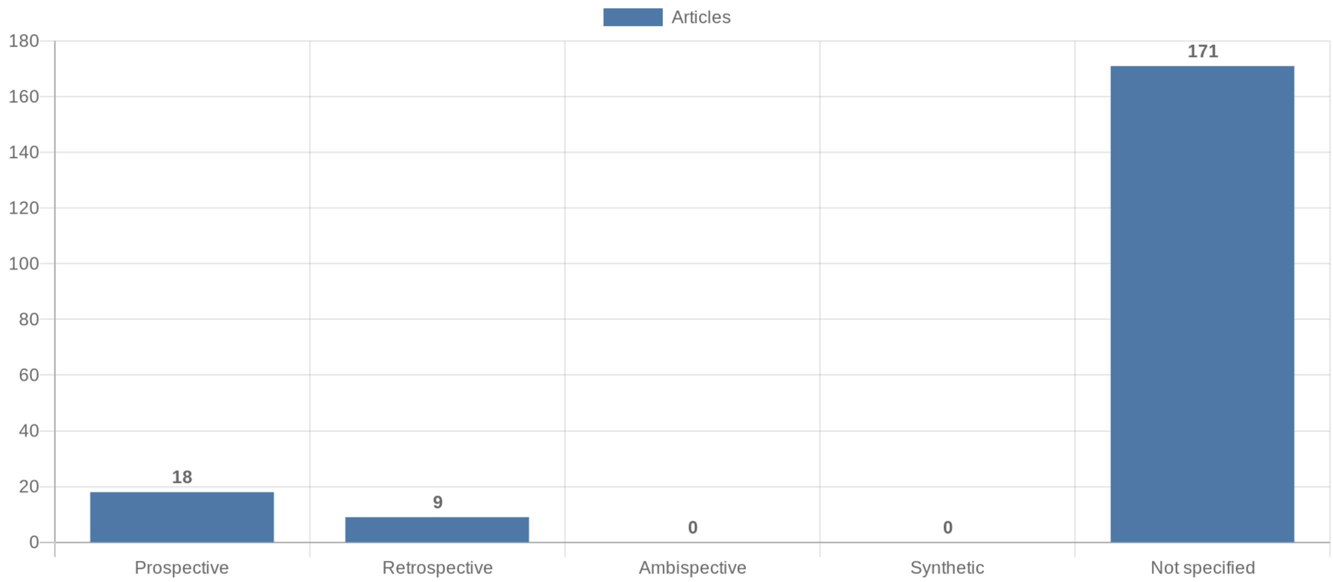

Figure 4. Main extracted research topics

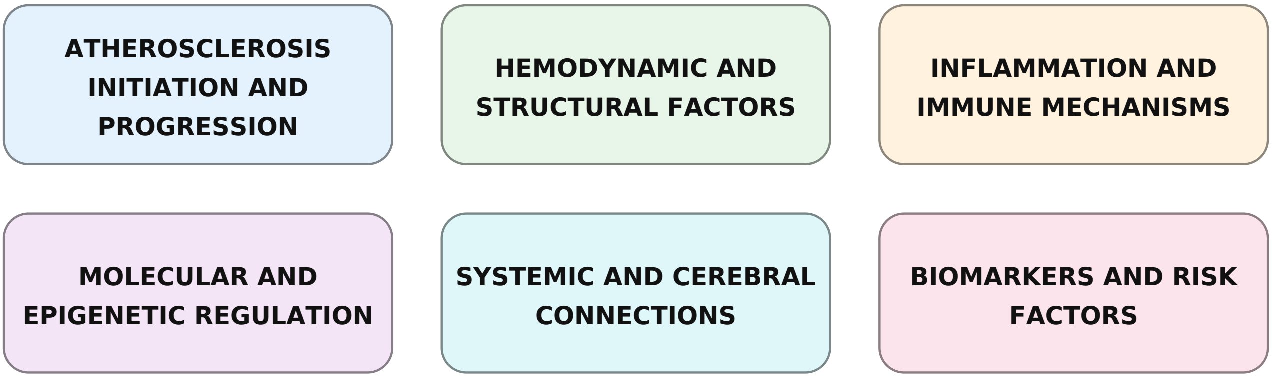

Figure 5. Limitations of current studies (topics)

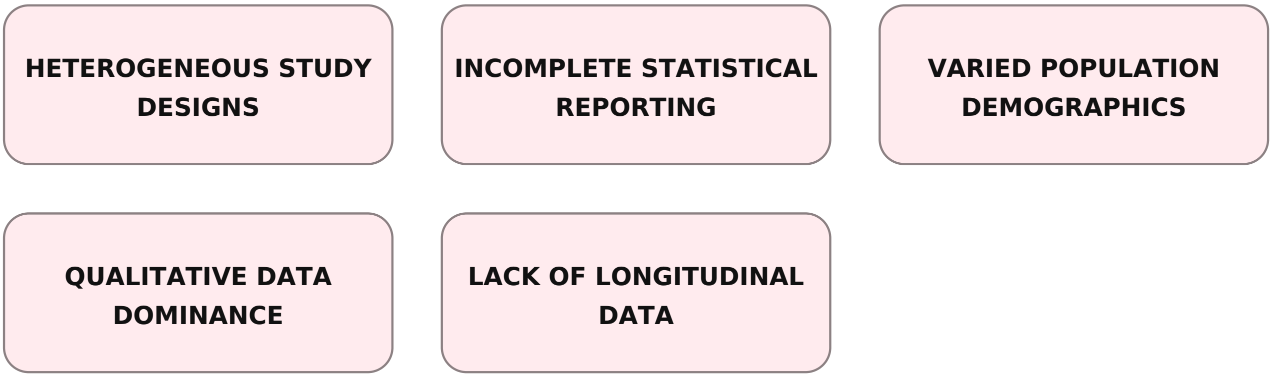

Figure 6. Future research directions (topics)