Carotid Stenosis Risk Factors: Systematic Review with ☸SAIMSARA.

Abstract: To systematically review and synthesize the identified risk factors for carotid stenosis based on a structured extraction summary of academic literature. The review utilises 154 studies with 270434 total participants (naïve ΣN). The prevalence of carotid artery stenosis varies significantly depending on the study population and diagnostic criteria, ranging from 0.56% in a large cohort of Chinese adults to 53.2% in patients presenting with cerebral infarction. Key risk factors include advanced age, male sex, hypertension, diabetes mellitus, dyslipidemia, and smoking, along with various co-morbidities and specific plaque characteristics. The most significant limitation affecting certainty is the heterogeneity of study populations and designs, which complicates the synthesis of a unified risk profile. Clinicians should maintain a high index of suspicion for carotid stenosis in older male patients with multiple traditional cardiovascular risk factors and consider comprehensive risk factor management.

Keywords: Carotid Stenosis; Risk Factors; Atherosclerosis; Hypertension; Diabetes Mellitus; Dyslipidemia; Smoking; Age; Ischemic Stroke; Cardiovascular Disease

Review Stats

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- Scope: All fields
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
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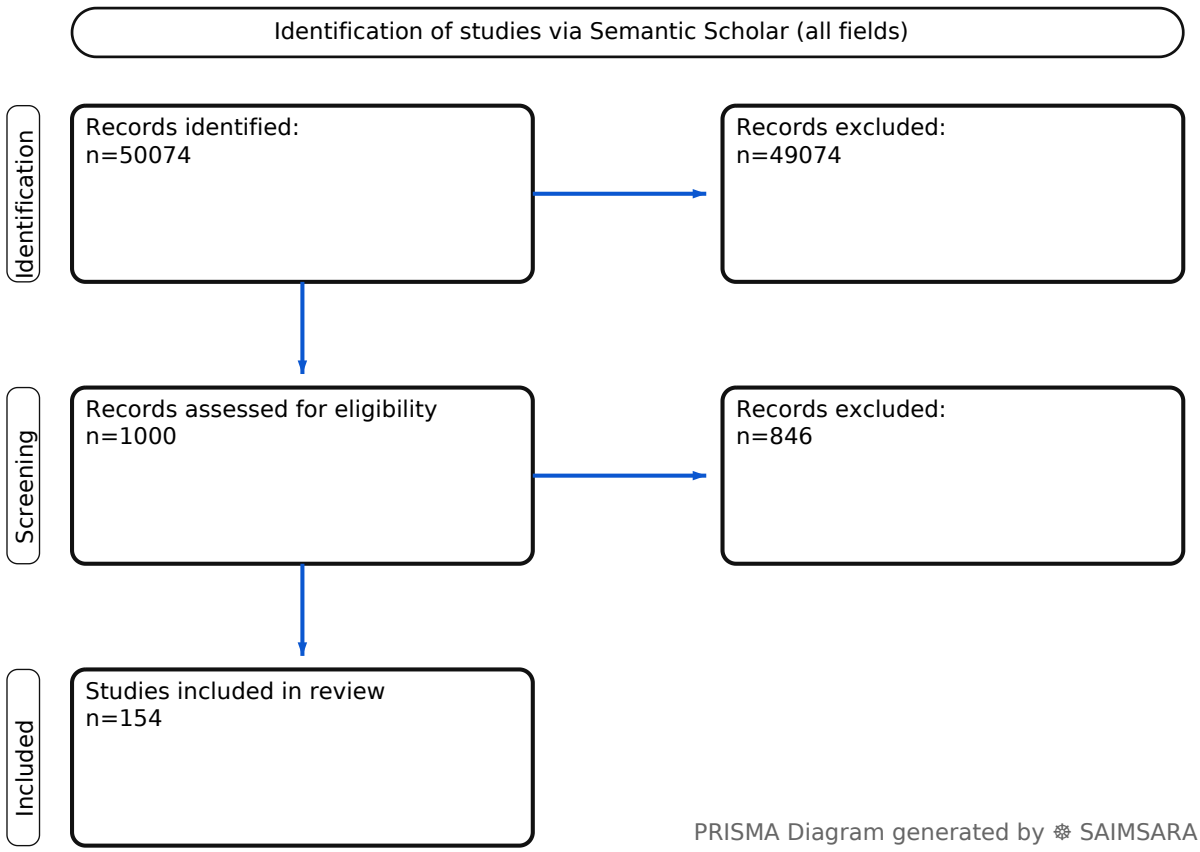
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 154
- Total study participants (naïve ΣN): 270434


Identification of studies via Semantic Scholar (all fields)
Identification
Records identified:
n=50074
Records excluded:
n=49074
Screening
Records assessed for eligibility
n=1000
Records excluded:
n=846
Included
Studies included in review
n=154
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
risk factors → carotid stenosis
0
Harmful for patients ΣN=201124 (74%)
Beneficial for patients ΣN=15980 (6%)
Neutral ΣN=53330 (20%)
△OSMA Triangle generated by ☸SAIMSARA

Outcome-Sentiment Meta-Analysis (OSMA): *(LLM-only)*
Frame: Effect-of Predictor → Outcome • *Source*: Semantic Scholar
Outcome: carotid stenosis Typical timepoints: peri/post-op, 5-y. Reported metrics: %, CI, p.
Common endpoints: Common endpoints: complications, mortality, occlusion.
Predictor: risk factors — exposure/predictor. Routes seen: intravenous, oral. Typical comparator: carotid endarterectomy, conventional methods, patients without stenosis, patients without restenosis….

- **1) Beneficial for patients** — carotid stenosis with risk factors — [10], [16], [39], [45], [93], [94] — ΣN=15980
- **2) Harmful for patients** — carotid stenosis with risk factors — [2], [4], [5], [6], [7], [8], [9], [11], [12], [13], [14], [15], [17], [18], [19], [20], [21], [22], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [40], [41], [42], [43], [44], [46], [47], [48], [50], [76], [77], [78], [79], [80], [84], [85], [86], [87], [88], [89], [90], [91], [95], [96], [97], [98], [99], [100], [101], [102], [103], [104], [105], [106], [107], [108], [109], [110], [111], [112], [113], [114], [117], [118], [119], [120], [121], [122], [123], [125], [127], [131], [132], [134], [136], [138], [139], [141], [144], [145], [146], [147], [148], [149], [150] — ΣN=201124
- **3) No clear effect** — carotid stenosis with risk factors — [1], [3], [23], [38], [49], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72], [73], [74], [75], [81], [82], [83], [92], [115], [116], [124], [126], [128], [129], [130], [133], [135], [137], [140], [142], [143], [151], [152], [153], [154] — ΣN=53330

1) **Introduction**

Carotid artery stenosis, a significant manifestation of atherosclerosis, is a leading cause of ischemic stroke and a marker of systemic vascular disease. Its presence is associated with increased morbidity and mortality, necessitating a comprehensive understanding of its underlying risk factors for effective prevention, diagnosis, and management. This paper synthesizes current research on factors contributing to the development and progression of carotid stenosis, drawing from a wide array of clinical studies.

2) **Aim**

To systematically review and synthesize the identified risk factors for carotid stenosis based on a structured extraction summary of academic literature.

3) **Methods**

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

- **Bias:** Qualitatively inferred from study design fields. The included studies predominantly comprise observational designs (cohort, cross-sectional, retrospective, mixed), which are susceptible to selection bias, confounding, and varying levels of evidence. Randomized controlled trials (RCTs) are less frequent, limiting strong causal inferences for many risk factors.

4) **Results**

4.1 **Study characteristics:**

The review included a diverse set of studies, primarily cohort (e.g., [1, 4, 10, 12, 13, 15, 16, 17, 20, 39, 48, 49, 54, 57, 62, 63, 64, 65, 66, 72, 74, 77, 78, 80, 84, 86, 90, 91, 100, 107, 109, 110, 111, 120, 121, 122, 124, 128, 130, 134, 137, 140, 141, 143, 144, 145, 147, 148, 149, 150, 151, 152, 153, 154]), cross-sectional (e.g., [2, 3, 11, 18, 75, 79, 81, 93, 95, 112, 114, 131, 136, 138, 151]), and mixed designs (e.g., [5, 6, 7, 8, 9, 21, 22, 23, 24, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 41, 42, 43, 44, 45, 46, 47, 50, 51, 55, 56, 59, 61, 67, 68, 69, 70, 71, 73, 76, 82, 85, 87, 88, 89, 92, 94, 96, 97, 98, 99, 101, 102, 103, 104, 105, 106, 108, 113, 115, 116, 117, 118, 119, 125, 126, 127, 129, 132, 133, 135, 139, 142, 146]). Populations ranged from general adults in specific regions (e.g., Chinese, Korean) to highly specific patient cohorts, such as those with ischemic stroke, ischemic heart disease (IHD), amaurosis fugax, or undergoing carotid artery stenting (CAS) or coronary artery bypass graft (CABG) surgery. Follow-up periods varied widely, from immediate post-procedure to over 10 years, with many cross-sectional studies having no follow-up.

4.2 **Main numerical result aligned to the query:**

The reported prevalence of carotid artery stenosis varies significantly depending on the study population and diagnostic criteria, ranging from 0.56% in a large cohort of Chinese adults [3] to 53.2% in patients presenting with cerebral infarction [111]. For specific patient groups, prevalence includes 13.5% in IHD patients undergoing CABG surgery [2], 12.5% in patients with recent transient ischaemic attack (TIA) or ischaemic stroke [4], and 18.9% in patients diagnosed with amaurosis fugax [8]. This heterogeneity precludes a single central value, highlighting the context-dependent nature of carotid stenosis prevalence.

4.3 **Topic synthesis:**

- **Demographic Factors:** Age is a dominant and consistently identified risk factor, with higher age (e.g., OR 1.79 per 10 years [2], OR 8.11 for ≥80 years [6]) increasing risk. Male

sex is also frequently associated (e.g., OR 2.8 [4], OR 2.16 [6], OR 2.62 [8]), while female gender is a risk factor for perioperative strokes after transcatheter aortic valve implantation (TAVI) (OR 2.25) [37] and higher recurrence rates post-carotid endarterectomy (CEA) [78]. Rural residence [114] and specific ethnic backgrounds, such as Native Americans (relative risk 1.53 compared to Whites) [93], are also noted.

- **Traditional Cardiovascular Risk Factors:** Hypertension is a highly prevalent risk factor (e.g., OR 2.38 for uncontrolled hypertension [2], OR 3.16 for hypertension [6], 79.39% abnormal carotid intima-media thickness (cIMT) rates [18]), directly correlated with stenosis severity [18, 131]. Diabetes mellitus is consistently implicated (e.g., OR 2.51 for uncontrolled DM [2], OR 3.68 [8]), with duration of diabetes also being important [17]. Dyslipidemia/hyperlipidemia, including high low-density lipoprotein cholesterol (LDL-C) (e.g., OR 2.19 for dyslipidemia [2], OR 1.84 for hyperlipidemia [6], OR 2.22 for Hyper-LDL-c [35]), and elevated non-fasting triglycerides [91] are significant. Smoking, both current (e.g., OR 1.8 [4], OR 6.26 [8]) and ex-smoking (OR 6.81) [6], is a strong predictor. Obesity (higher BMI [66]) and physical inactivity [114] also contribute.
- **Co-morbidities and Systemic Conditions:** Ischemic heart disease (IHD) and coronary artery disease (CAD) are frequently linked (e.g., multivessel CAD OR 3.79 [2], 77.5% prevalence of CAD in patients with carotid stenosis [68]). A history of stroke or transient ischemic attack (TIA) [4, 24, 111] and peripheral artery disease (PAD) [21, 24, 97] are significant. Renal failure, including decreased estimated glomerular filtration rate (eGFR) [10, 62], and metabolic-associated fatty liver disease (MAFLD) [17] are also risk factors. Cytomegalovirus (CMV) DNA positivity is higher in patients with diabetes, hypertension, and bilateral carotid artery stenosis [29]. Radiation therapy for nasopharyngeal carcinoma (NPC) is a specific risk factor, with age, radiation technique, and time interval from RT being independent predictors [28, 73].
- **Inflammatory and Biochemical Markers:** Elevated C-reactive protein (CRP) [1, 95, 134], interleukin-6 (IL-6) [46], Pentraxin 3 (PTX3), and Tumor Necrosis Factor-alpha (TNF-α) [102] are associated with carotid stenosis and plaque vulnerability. High plasma levels of homocysteine [99, 136, 148] and lipoprotein(a) [89, 108] are independent risk factors. Impaired cholesterol homeostasis, characterized by lower cholesterol synthesis and higher cholesterol absorption markers, also predicts prevalent cardiovascular disease (CVD) in patients with carotid stenosis [80].
- **Plaque Characteristics and Progression:** Plaque volume [19, 121, 122], increased carotid intima-media thickness (cIMT) [3, 15, 18, 100], and specific plaque morphologies contribute to risk. Irregular plaques [7], calcification [7, 19, 33], intraplaque hemorrhage (IPH) [48, 61, 74, 117, 125, 128, 150], and intraplaque neovascularization (IPN) [86, 89, 139] are associated with plaque vulnerability and ischemic events. Eccentric stenosis is linked to a significantly increased incidence of ipsilateral cerebrovascular events [132]. Progression of

stenosis is associated with higher stenosis grade [35] and non-fasting triglyceride levels [91].

- **Genetic Predisposition:** Gene-gene interactions among TXA2R, P2Y1, and GPIIIa show a synergistic influence on carotid stenosis [13]. APOE genotype is associated with carotid atherosclerosis, with the E2 allele linked to lower IMT and stenosis in women [77]. The FSAP-Marburg I polymorphism is associated with increased stroke risk and mortality [145]. The NAV1 gene is a susceptibility gene for calcific aortic valve stenosis, with its risk allele colocalizing with higher prevalence of carotid artery stenosis [135].

5) **Discussion**

5.1 **Principal finding:** The prevalence of carotid artery stenosis is highly variable, ranging from 0.56% in general adult populations to over 50% in patients with cerebral infarction [3, 111], with age being the most consistently identified and dominant risk factor across diverse populations and study designs.

5.2 **Clinical implications:**

- **Targeted Screening:** Given the strong association of age, male sex, hypertension, diabetes, and smoking with carotid stenosis, screening efforts should prioritize individuals with these risk factors, especially those with existing cardiovascular disease or symptoms like amaurosis fugax [2, 4, 8, 14].
- **Intensive Risk Factor Management:** Aggressive management of traditional cardiovascular risk factors, including blood pressure, lipids (LDL-C, triglycerides), and glucose control, is crucial for preventing and potentially regressing carotid atherosclerosis [16, 17, 130]. Smoking cessation is paramount [4, 8].
- **Plaque Characterization:** Beyond stenosis degree, advanced imaging techniques that characterize plaque morphology (e.g., irregular plaques, calcification, intraplaque hemorrhage, neovascularization) can help identify vulnerable plaques and stratify stroke risk, guiding treatment decisions [7, 74, 86, 150].
- **Post-Procedural Monitoring:** Patients undergoing carotid artery stenting (CAS) or carotid endarterectomy (CEA) require close monitoring for restenosis, particularly those with bilateral or high-grade stenosis, male sex, smoking, and hyperlipidemia [9, 12]. Inflammatory biomarkers may also predict restenosis [113].
- **Cognitive Assessment:** Patients with severe asymptomatic carotid stenosis are at risk for poorer cognitive function, particularly in memory domains [96, 109], suggesting that cognitive assessment may be warranted in this population.

5.3 **Research implications / key gaps:**

- **Standardized Risk Models:** Development and validation of standardized, integrated risk prediction models for carotid stenosis progression and associated stroke risk across diverse populations, incorporating both traditional and novel biomarkers (e.g., genetic, inflammatory, plaque features) [38, 94, 95].
- **Longitudinal Plaque Dynamics:** Prospective longitudinal studies are needed to better understand the dynamic interplay between systemic risk factors, plaque composition, and the natural history of stenosis progression, particularly in asymptomatic individuals [35, 46, 90].
- **Genetic-Environment Interactions:** Further research into specific gene-environment interactions (e.g., APOE genotype, FSAP-Marburg I polymorphism) that modulate carotid atherosclerosis risk and treatment response is warranted to enable personalized prevention strategies [13, 77, 145].
- **Impact of Novel Biomarkers:** Large-scale prospective studies are needed to confirm the clinical utility and cost-effectiveness of novel biomarkers (e.g., CRP, IL-6, PTX3, TNF-α, Lp(a), homocysteine, miR-638) in predicting carotid stenosis development, progression, and stroke risk beyond traditional factors [1, 46, 89, 94, 95, 99, 102, 108, 136, 148].
- **Intervention Efficacy in Specific Subgroups:** Randomized controlled trials are needed to evaluate the efficacy of intensive medical therapy or revascularization strategies in specific high-risk subgroups, such as patients with MAFLD [17], post-radiotherapy for NPC [28], or those with specific plaque vulnerabilities (e.g., intraplaque hemorrhage, neovascularization) [86, 128].

5.4 **Limitations:**

- **Heterogeneous Populations** — The wide variety of study populations (general, specific disease cohorts, post-procedure) limits the generalizability of specific prevalence rates and risk factor magnitudes.
- **Varied Study Designs** — A predominance of observational studies (cohort, cross-sectional, retrospective) introduces potential for selection bias and confounding, hindering strong causal inferences.
- **Inconsistent Definitions** — Different definitions of "significant stenosis" (e.g., >50%, >70%, >80%) and methods of assessment across studies make direct comparisons challenging.
- **Qualitative Bias Inference** — Bias was qualitatively inferred from study design, not formally assessed using a standardized tool, which may understate methodological weaknesses.

- **Lack of Follow-up** — Many studies were cross-sectional or had limited follow-up, preventing a clear understanding of long-term risk factor impact or disease progression.

5.5 **Future directions:**

- **Standardized Diagnostic Criteria** — Establish uniform criteria for carotid stenosis diagnosis and severity grading to improve comparability across studies.
- **Longitudinal Cohort Studies** — Conduct large-scale, long-term prospective cohort studies in diverse populations to track stenosis progression and outcomes.
- **Multi-Omics Integration** — Integrate genetic, proteomic, and metabolomic data with clinical risk factors to develop more precise risk prediction models.
- **Advanced Imaging Biomarkers** — Validate novel imaging biomarkers (e.g., plaque stiffness, wall shear stress, micro-flows) for predicting plaque vulnerability and stroke risk.
- **Personalized Intervention Trials** — Design clinical trials that test tailored interventions based on individual risk profiles, including genetic predispositions and plaque characteristics.

6) **Conclusion**

The prevalence of carotid artery stenosis varies significantly depending on the study population and diagnostic criteria, ranging from 0.56% in a large cohort of Chinese adults [3] to 53.2% in patients presenting with cerebral infarction [111]. Key risk factors include advanced age, male sex, hypertension, diabetes mellitus, dyslipidemia, and smoking, along with various co-morbidities and specific plaque characteristics. The most significant limitation affecting certainty is the heterogeneity of study populations and designs, which complicates the synthesis of a unified risk profile. Clinicians should maintain a high index of suspicion for carotid stenosis in older male patients with multiple traditional cardiovascular risk factors and consider comprehensive risk factor management.

References

SAIMSARA Session Index — session.json

Figure 1. Publication-year distribution of included originals

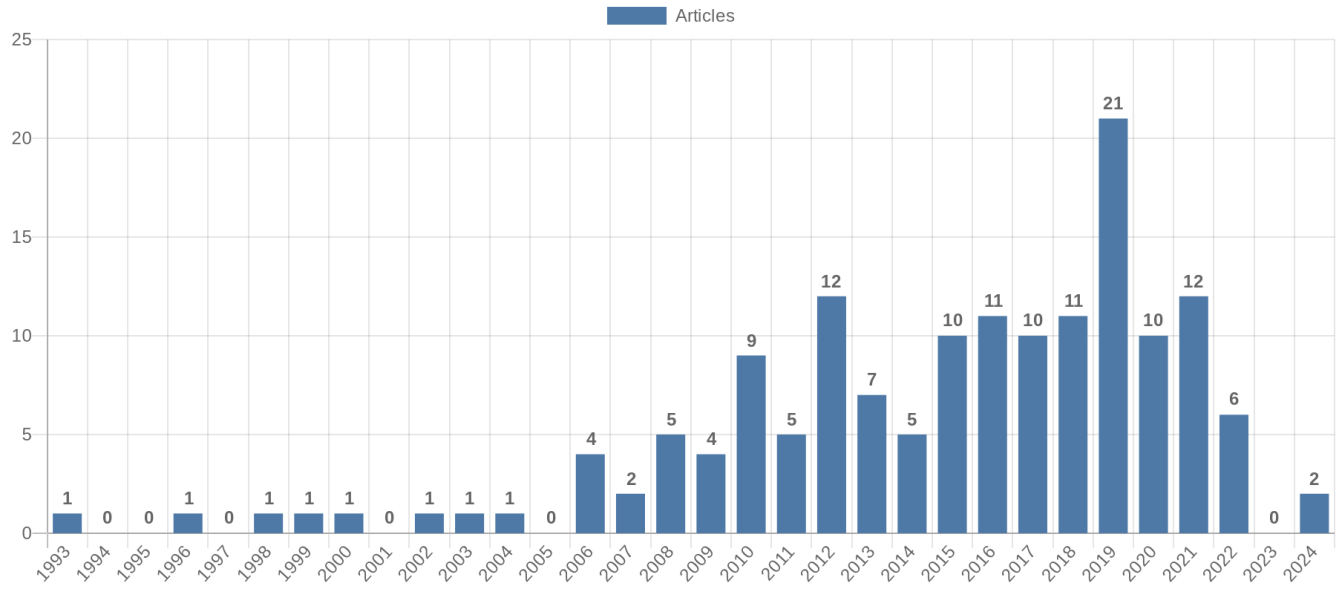


Figure 2. Study-design distribution of included originals

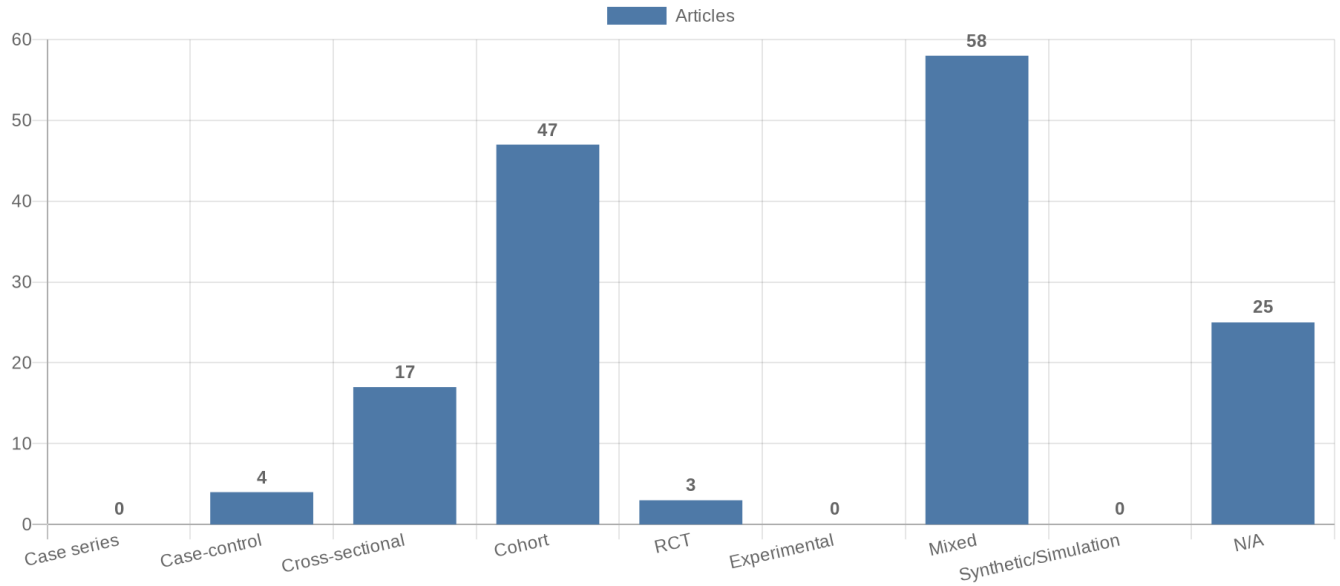


Figure 3. Study-type (directionality) distribution of included originals

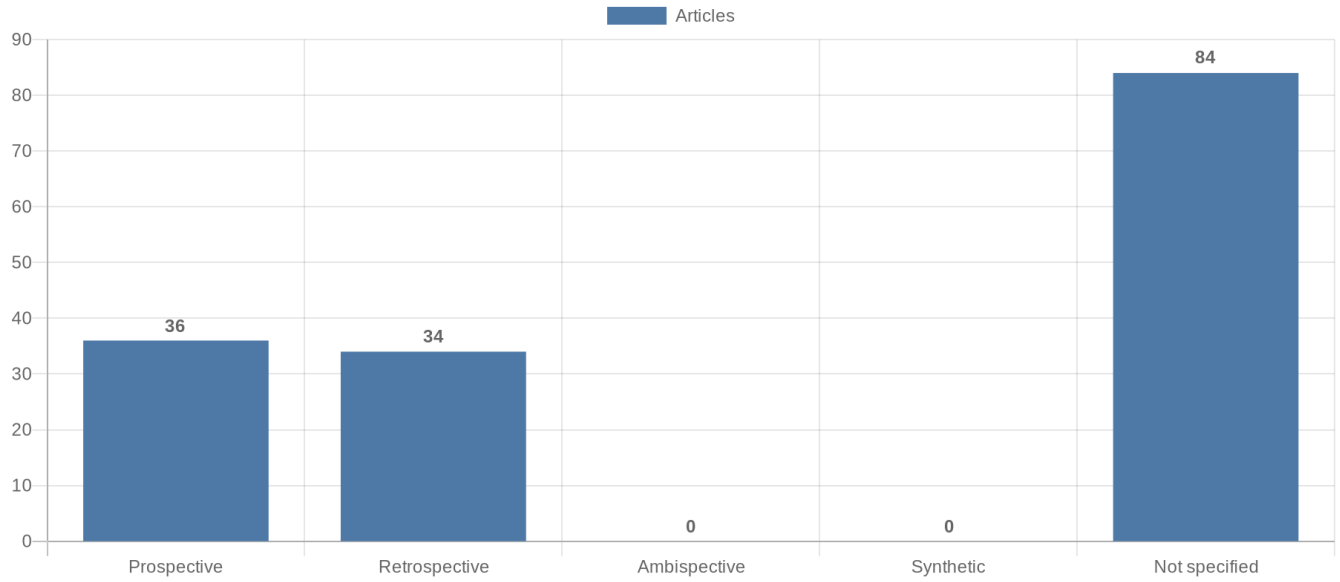


Figure 4. Main extracted research topics

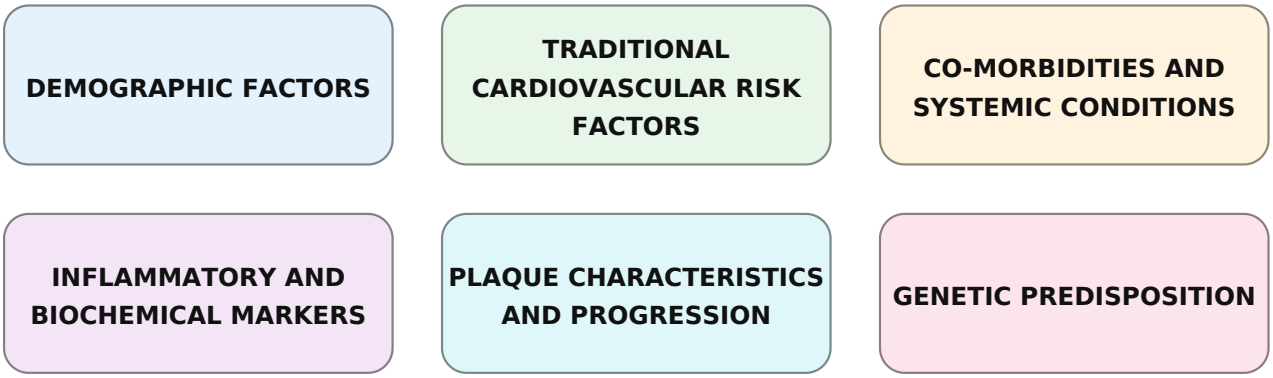


Figure 5. Limitations of current studies (topics)

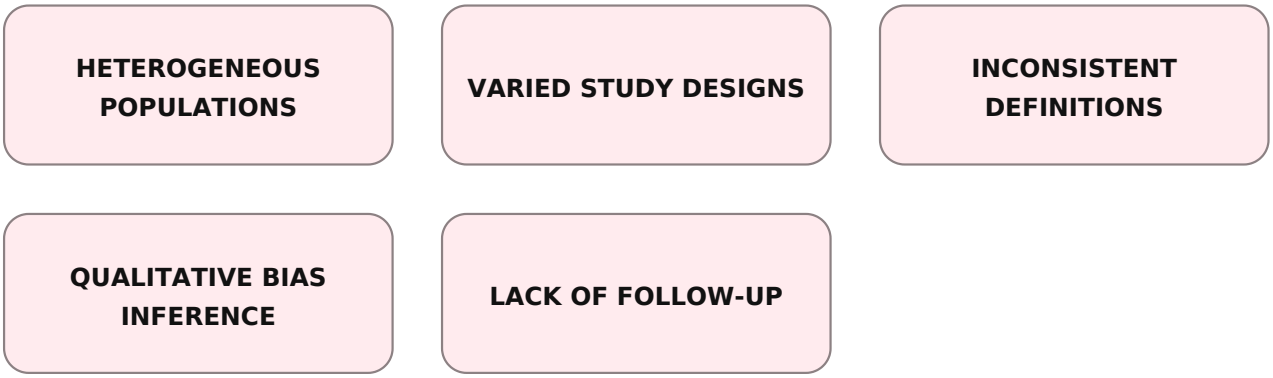


Figure 6. Future research directions (topics)