Asymptomatic Carotid Stenosis: Systematic Review with ☸SAIMSARA.

Abstract: This paper aims to systematically synthesize the diverse findings related to asymptomatic carotid stenosis, extracting key themes from the provided structured literature summary to illuminate its prevalence, pathophysiology, clinical manifestations, diagnostic approaches, and therapeutic strategies, ultimately identifying current knowledge gaps and future research directions. The review utilises 222 studies with 56552 total participants (naïve ΣN). A prospective randomized controlled trial indicated that 10% to 12% of asymptomatic patients will experience a symptomatic stroke within 5 years, underscoring the inherent risk despite the lack of symptoms. This risk, coupled with observed cognitive impairments and cerebral hypoperfusion, necessitates careful consideration of management strategies. The heterogeneity of study designs and patient populations represents the primary limitation to drawing definitive conclusions. Clinicians should integrate advanced plaque imaging and hemodynamic assessments into risk stratification, moving beyond simple stenosis degree. A crucial next step is to conduct large-scale randomized controlled trials to definitively assess the impact of revascularization on long-term cognitive outcomes in asymptomatic patients.

Keywords: Asymptomatic Carotid Stenosis; Cognitive Impairment; Stroke Prevention; Car

Review Stats

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- Scope: All fields
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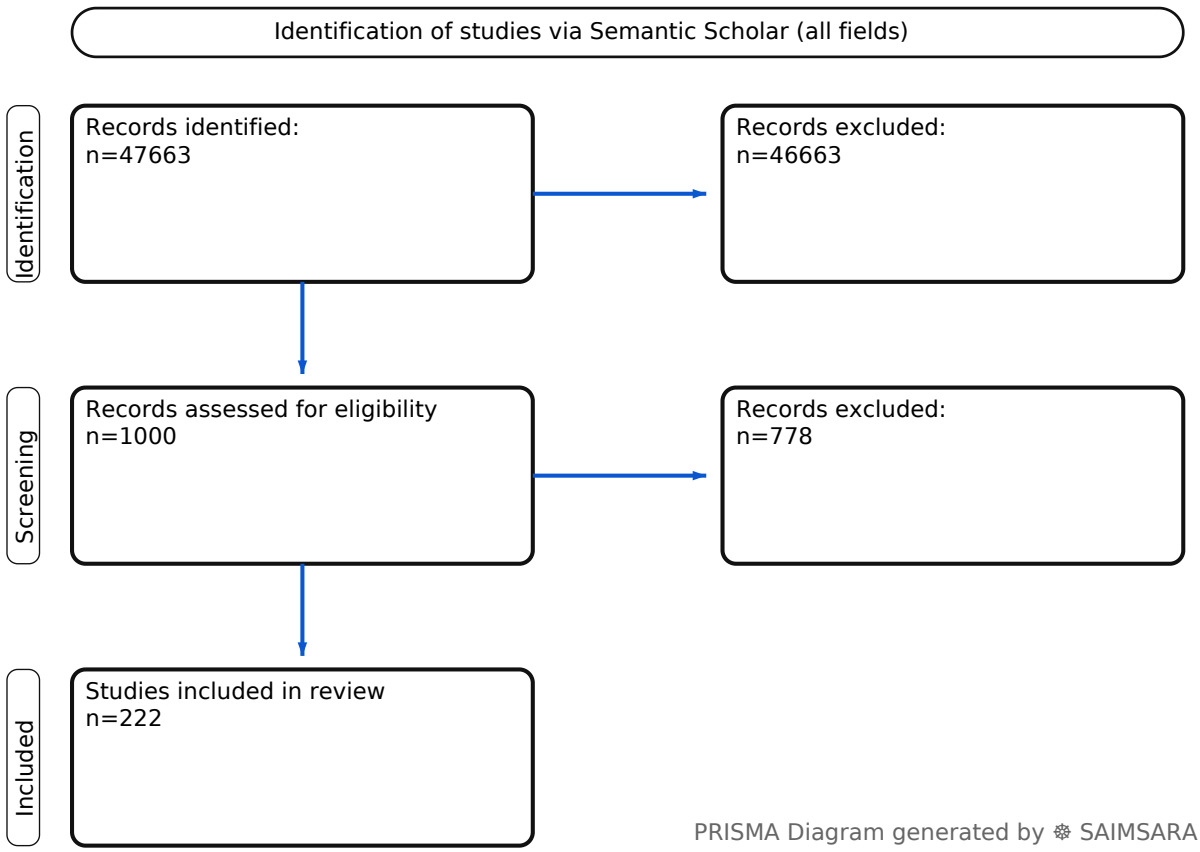
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 222
- Total study participants (naïve ΣN): 56552


Identification of studies via Semantic Scholar (all fields)
Identification
Records identified:
n=47663
Records excluded:
n=46663
Screening
Records assessed for eligibility
n=1000
Records excluded:
n=778
Included
Studies included in review
n=222
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
asymptomatic carotid stenosis → Outcome
0
Harmful for patients ΣN=2114 (4%)
Beneficial for patients ΣN=446 (1%)
Neutral ΣN=53992 (95%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: Outcome Typical timepoints: 5-y, 30-day. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, mortality, occlusion.

Predictor: asymptomatic carotid stenosis — exposure/predictor. Routes seen: intravenous.

Typical comparator: a population-based cohort, controls, healthy controls, endarterectomy for….

- **1) Beneficial for patients** — Outcome with asymptomatic carotid stenosis — [5], [11], [12], [23], [41], [149], [199] — ΣN=446
- **2) Harmful for patients** — Outcome with asymptomatic carotid stenosis — [2], [3], [4], [6], [16], [25], [28], [42], [43], [135], [139], [185], [197] — ΣN=2114
- **3) No clear effect** — Outcome with asymptomatic carotid stenosis — [1], [7], [8], [9], [10], [13], [14], [15], [17], [18], [19], [20], [21], [22], [24], [26], [27], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [44], [45], [46], [47], [48], [49], [50], [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], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94], [95], [96], [97], [98], [99], [100], [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], [136], [137], [138], [140], [141], [142], [143], [144], [145], [146], [147], [148], [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], [186], [187], [188], [189], [190], [191], [192], [193], [194], [195], [196], [198], [200], [201], [202], [203], [204], [205], [206], [207], [208], [209], [210], [211], [212], [213], [214], [215], [216], [217], [218], [219], [220], [221], [222] — ΣN=53992

1) Introduction

Asymptomatic carotid stenosis (ACS) represents a significant clinical challenge due to its silent nature and potential for severe cerebrovascular events, including stroke. While the presence of carotid artery narrowing is identifiable through various imaging modalities, the absence of overt neurological symptoms complicates risk stratification and management decisions. Research into ACS spans decades, evolving from early surgical interventions to contemporary investigations into underlying

pathophysiology, advanced imaging biomarkers, cognitive implications, and comparative effectiveness of medical and procedural treatments. Understanding the natural history, identifying high-risk plaque features, and optimizing patient selection for intervention remain central to improving outcomes for individuals with ACS.

2) Aim

This paper aims to systematically synthesize the diverse findings related to asymptomatic carotid stenosis, extracting key themes from the provided structured literature summary to illuminate its prevalence, pathophysiology, clinical manifestations, diagnostic approaches, and therapeutic strategies, ultimately identifying current knowledge gaps 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:** Qualitatively inferred from study design fields. The included studies exhibit a qualitative bias towards observational cohort designs and mixed study types, with fewer large-scale randomized controlled trials (RCTs) providing definitive comparative outcomes. Many studies involve relatively small sample sizes, particularly for investigations into cognitive and plaque characteristics, potentially limiting generalizability. The heterogeneity in patient populations, definitions of stenosis severity, and follow-up durations across studies also introduces variability in reported results.

4) Results

4.1 Study characteristics:

The extracted literature comprises a wide range of study designs, predominantly cohort studies and mixed designs, with several randomized controlled trials and case-control studies. Populations varied from general health screening cohorts to specific patient groups, including those with peripheral arterial disease, diabetes mellitus, or those undergoing coronary artery bypass grafting. Sample sizes ranged from single case reports to large cohorts of over 20,000 individuals, with typical follow-up periods varying from immediate post-procedure assessment to long-term observations spanning up to 10 years, though many studies did not specify follow-up duration.

4.2 Main numerical result aligned to the query:

A single comparable numeric outcome for asymptomatic carotid stenosis across the heterogeneous studies is not consistently reported in a format suitable for aggregation (median and range). However, a prospective randomized controlled trial indicated that 10% to 12% of asymptomatic

patients will experience a symptomatic stroke within 5 years [190]. Another prospective study reported an 11.7% rate of ipsilateral ischemic cerebrovascular events over a median follow-up of 41.1 months in patients with 50-99% asymptomatic carotid artery stenosis [139].

4.3 Topic synthesis:

- **Cognitive Impairment and Brain Structure:** Patients with severe asymptomatic carotid stenosis (SACS) often exhibit below-normal cognition [3], worse verbal memories, higher white matter hyperintensity (WMH) burden, and altered gray matter regions compared to controls [4]. Functional connectivity of neural oscillations is significantly decreased prior to revascularization, normalizing after the procedure [5], and revascularization can partly improve cognition [11, 12, 69]. Hemodynamic impairment, such as TTP delay on MRI, is associated with relative cortical thinning [1], and lower blood flow correlates with thinner cortex in affected hemispheres [27].
- **Plaque Vulnerability and Stroke Risk Prediction:** Intraplaque neovascularization (Grade 2) independently predicts future ischemic events (Hazard Ratio: 4.530, 95% Confidence Interval: 1.337–15.343) [2]. High-risk plaque features, including thin/ruptured fibrous cap, intraplaque hemorrhage (IPH), and lipid-rich necrotic core (LRNC), are associated with symptomatic events [63, 64, 192, 193, 194, 195, 218]. Asymptomatic patients with unstable plaques show higher levels of endothelial microparticles (EMPs), CXCL9, and SCGF-β [87]. Combining ultrasound elastography and echogenicity can discriminate vulnerable plaques with 71.6% sensitivity and 79.3% specificity [186], while plaques in asymptomatic patients tend to have higher mean Young's Modulus (88 kPa vs 62 kPa; p=0.01) [220].
- **Hemodynamic Impairment and Cerebral Perfusion:** Asymptomatic carotid artery stenosis is associated with cerebral hypoperfusion [25], with lower blood flow and thinner cortex observed on the ipsilateral side of occlusion [27]. Carotid stent placement has been shown to improve cerebral blood flow (CBF) in asymptomatic patients [89]. Hemispherical asymmetry in arterial transit time (ATT) and flow territory are better predictors of high-grade internal carotid artery (ICA) stenosis than CBF [91]. Impaired cerebrovascular reactivity is a predictor of stroke risk [43, 155], and both cerebral autoregulation (CA) and baroreflex sensitivity (BRS) are impaired in patients with carotid stenosis [212].
- **Revascularization Strategies and Outcomes:** Carotid endarterectomy (CEA) has demonstrated efficacy in reducing stroke risk for ACS [9, 101, 199], with contemporary results showing favorable stroke-free rates [102]. Transcarotid artery revascularization (TCAR) was associated with a significantly lower risk of in-hospital stroke or death (1.6% vs 3.1%; $P < .001$) and ipsilateral stroke or death at 1 year (5.1% vs 9.6%; Hazard Ratio, 0.52; $P < .001$) compared to transfemoral carotid artery stenting (TF-CAS) [61, 138]. The SPACE-2 trial found no significant difference in 1-year stroke or death rates between CEA, carotid

artery stenting (CAS), or best medical treatment (BMT) alone, although it was prematurely stopped due to low recruitment [20].

- **Inflammatory Markers and Plaque Biology:** Inflammatory markers such as erythrocyte aggregation (EA) and erythrocyte sedimentation rate (ESR) are more sensitive in detecting significant atherosclerotic carotid burden than high-sensitivity C-reactive protein (hs-CRP) [56]. Low HDL-cholesterol is an independent predictor of symptomatic carotid artery stenosis (Odds Ratio: 1.81, 95% CI: 1.15-2.84, p=0.01) [66]. Symptomatic plaques show increased platelet count and leukocyte-platelet complex formation [67], and higher levels of endothelial microparticles (EMPs) and specific chemokines (CXCL9, SCGF-β) in unstable plaques [87].
- **Prevalence and Risk Factors:** The prevalence of asymptomatic carotid stenosis varies by population and stenosis degree, with rates such as 4.2% for >50% stenosis in asymptomatic Russians [210], and up to 14% for ≥70% ICA stenosis in Korean patients with peripheral arterial disease [95]. Key risk factors include old age, male gender, hypertension, diabetes mellitus, and ischemic heart disease [48, 88]. Diabetes significantly increases mortality risk in asymptomatic patients with carotid stenosis (adjusted HR 1.62 for all-cause, 1.75 for cardiovascular) [185].
- **Screening and Diagnostic Modalities:** Duplex ultrasonography is widely used for screening and predicting stenosis [78, 123, 184], with specific criteria to differentiate stenosis degrees [105]. Advanced imaging techniques like MRI (for TTP delay and plaque features) [1, 139, 192], CT angiography (for plaque thickness and perivascular fat density) [136, 154, 209, 215], and Superb Microvascular Imaging (SMI) for neovessels [145] are utilized to characterize plaque vulnerability and hemodynamic impairment. Serum miR-28-5p has shown high diagnostic value (sensitivity 86.8%, specificity 81.5%) as a biomarker [59].

5) Discussion

5.1 Principal finding:

A prospective randomized controlled trial indicated that 10% to 12% of asymptomatic patients will experience a symptomatic stroke within 5 years [190], highlighting the non-negligible risk associated with asymptomatic carotid stenosis despite the absence of overt symptoms.

5.2 Clinical implications:

- **Risk Stratification Refinement:** Traditional stenosis degree alone is insufficient for predicting stroke risk; incorporating advanced plaque imaging features (e.g., intraplaque neovascularization, lipid-rich necrotic core, plaque echolucency) can better identify high-risk

asymptomatic patients who might benefit from intervention [2, 23, 139, 218].

- **Cognitive Monitoring:** Asymptomatic carotid stenosis is associated with cognitive decline and changes in brain structure and function; routine cognitive assessment could identify a subgroup of "symptomatic" patients who might benefit from revascularization [3, 4, 6, 109, 110].
- **Revascularization Modality Selection:** Transcarotid artery revascularization (TCAR) appears to offer lower periprocedural and 1-year stroke/death rates compared to transfemoral carotid artery stenting (TF-CAS) for carotid stenosis [61, 138], while carotid endarterectomy (CEA) may be associated with lower inpatient mortality, readmission rates, and hospital costs compared to CAS [149].
- **Intensive Medical Management:** Aggressive medical therapy alone can preserve cognition in severe asymptomatic carotid stenosis [12] and improve risk factor control, potentially offering a viable alternative or adjunct to revascularization [20, 211].
- **Biomarker Utility:** Novel biomarkers, such as serum miR-28-5p, and inflammatory markers, like low HDL-cholesterol, show promise in identifying high-risk plaques and predicting symptomatic status, potentially aiding clinical decision-making [59, 66].

5.3 Research implications / key gaps:

- **Standardized Biomarker Validation:** Future prospective cohort studies are needed to validate the utility and cost-effectiveness of advanced plaque imaging (e.g., MRI-based lipid core, 18F-FDG PET/CT uptake, SWE) and circulating biomarkers (e.g., miR-28-5p, inflammatory markers) for predicting stroke risk in diverse asymptomatic populations [59, 139, 194, 218, 220].
- **Cognitive Endpoint Trials:** Large-scale randomized controlled trials are needed to definitively assess whether revascularization alters the course of cognitive decline in asymptomatic carotid stenosis patients, using standardized, long-term cognitive endpoints [7, 12].
- **Comparative Effectiveness of Revascularization:** Ongoing and future RCTs, like ACST-2 and CREST2, should aim for robust recruitment and long-term follow-up to provide definitive comparisons of procedural risks and long-term stroke prevention between CEA, CAS, TCAR, and optimal medical therapy alone in specific asymptomatic patient subgroups [20, 60, 86, 211].
- **Hemodynamic Impairment Thresholds:** Research is needed to establish clear thresholds for hemodynamic impairment (e.g., TTP delay, cerebrovascular reactivity, wall shear stress) that reliably predict future ischemic events and guide intervention decisions in asymptomatic patients [1, 43, 57, 91, 155].

- **AI-driven Risk Stratification:** Development and validation of artificial intelligence (AI) models that integrate clinical, imaging, and biomarker data to provide personalized stroke risk prediction and treatment recommendations for asymptomatic carotid stenosis patients [108].

5.4 Limitations:

- **Heterogeneity of Studies** — The wide variety of study designs, patient populations, and diagnostic criteria limits direct comparison and synthesis of numerical outcomes.
- **Small Sample Sizes** — Many studies investigating cognitive changes or specific plaque characteristics involve small cohorts, which may affect the statistical power and generalizability of findings.
- **Variable Follow-up Durations** — Inconsistent follow-up periods across studies make it challenging to assess long-term outcomes and the natural history of the disease comprehensively.
- **Surrogate Endpoints** — A reliance on surrogate imaging markers (e.g., plaque features, cerebral hypoperfusion) rather than hard clinical endpoints (e.g., stroke, death) in some studies may not directly translate to patient benefit.
- **Lack of Standardized Definitions** — Definitions of "asymptomatic" and various degrees of stenosis (e.g., NASCET vs. ECST criteria) can vary, complicating the interpretation and comparison of results.

5.5 Future directions:

- **Large-Scale RCTs** — Conduct large-scale randomized controlled trials comparing intervention strategies with optimal medical therapy in well-defined asymptomatic patient subgroups.
- **Standardized Imaging Biomarkers** — Develop and validate standardized imaging biomarkers for plaque vulnerability and cerebral hemodynamics to improve risk stratification.
- **Longitudinal Cognitive Studies** — Perform long-term longitudinal studies to track cognitive function and brain structural changes in asymptomatic carotid stenosis patients, with and without intervention.
- **Cost-Effectiveness Analyses** — Conduct comprehensive cost-effectiveness analyses of different management strategies for asymptomatic carotid stenosis, considering both clinical outcomes and quality of life.

- **Personalized Risk Models** — Create and validate personalized risk prediction models integrating clinical, genetic, and multi-modal imaging data to guide individualized treatment decisions.

6) Conclusion

A prospective randomized controlled trial indicated that 10% to 12% of asymptomatic patients will experience a symptomatic stroke within 5 years [190], underscoring the inherent risk despite the lack of symptoms. This risk, coupled with observed cognitive impairments and cerebral hypoperfusion, necessitates careful consideration of management strategies. The heterogeneity of study designs and patient populations represents the primary limitation to drawing definitive conclusions. Clinicians should integrate advanced plaque imaging and hemodynamic assessments into risk stratification, moving beyond simple stenosis degree. A crucial next step is to conduct large-scale randomized controlled trials to definitively assess the impact of revascularization on long-term cognitive outcomes in asymptomatic patients.

References

SAIMSARA Session Index — session.json

Figure 1. Publication-year distribution of included originals

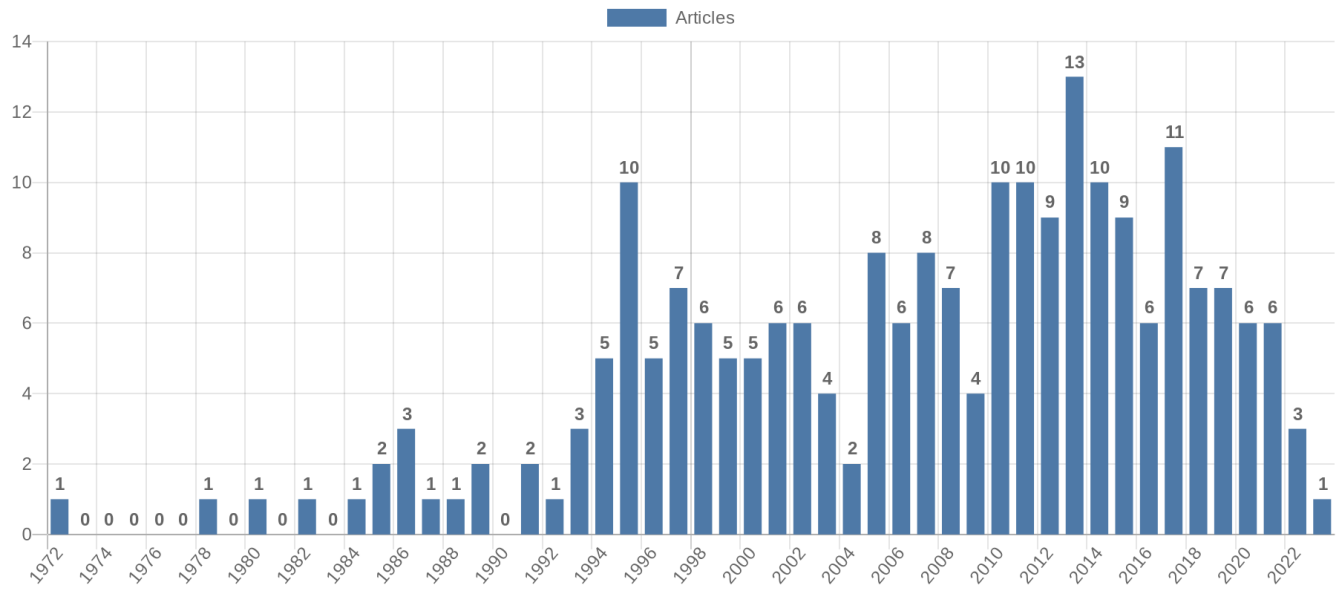


Figure 2. Study-design distribution of included originals

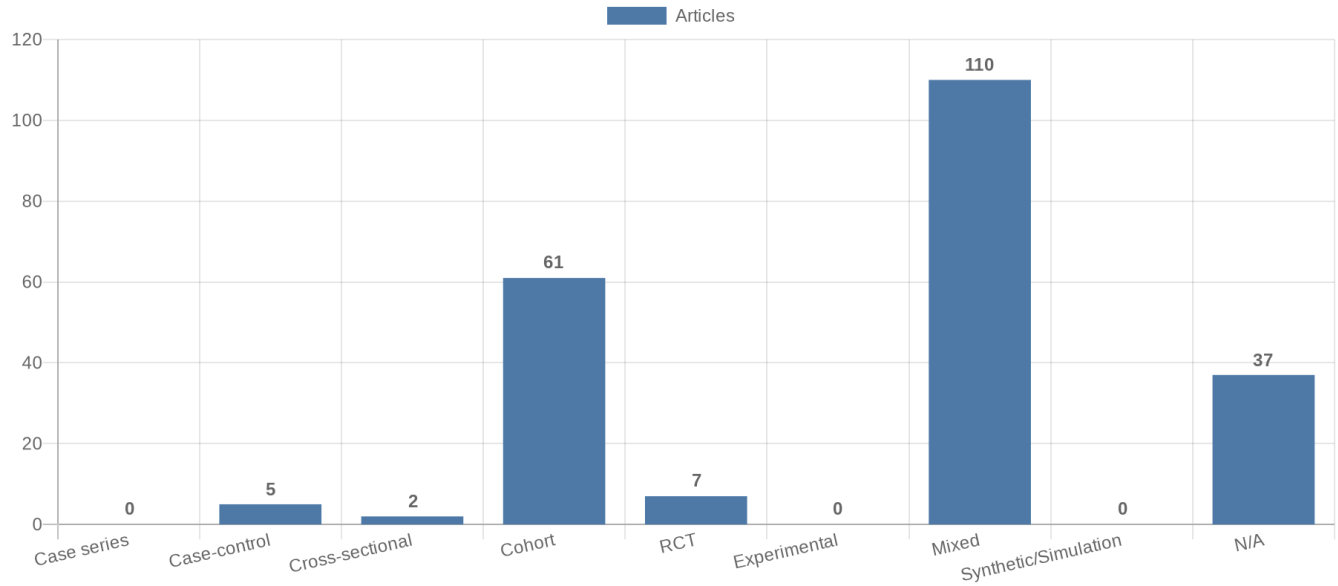


Figure 3. Study-type (directionality) distribution of included originals

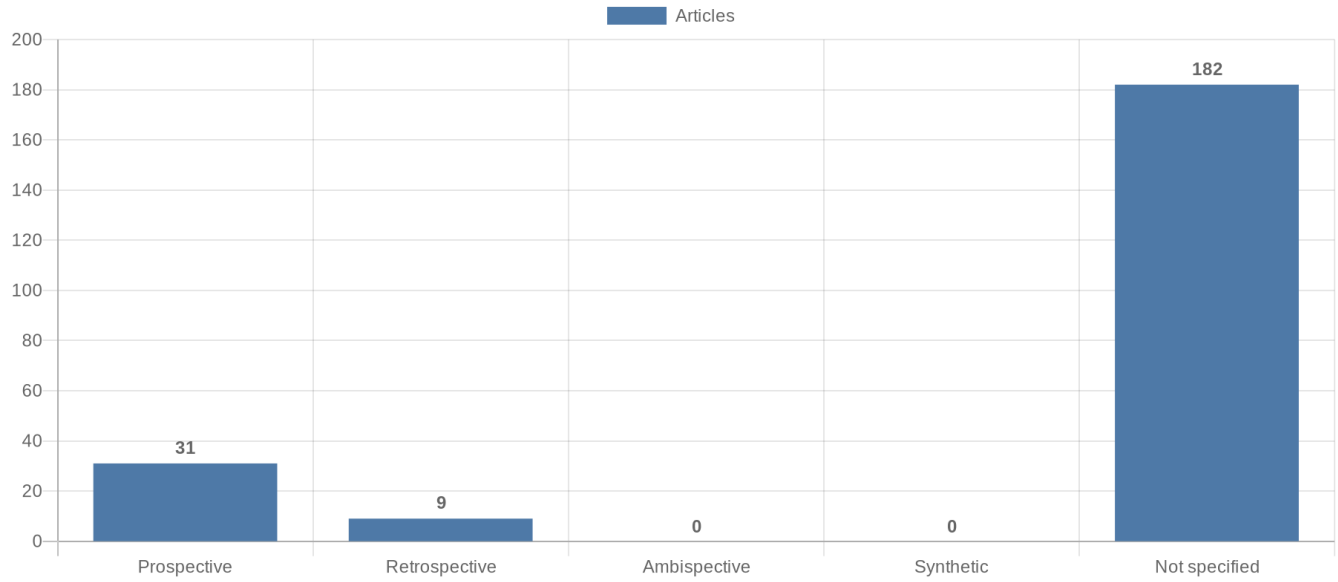


Figure 4. Main extracted research topics

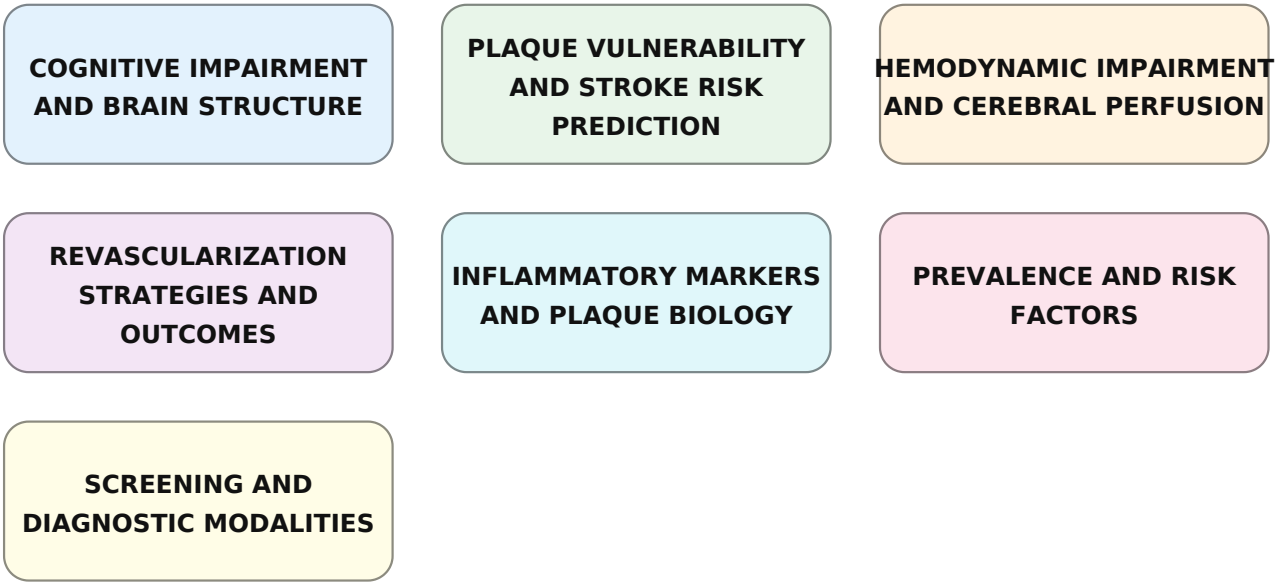


Figure 5. Limitations of current studies (topics)

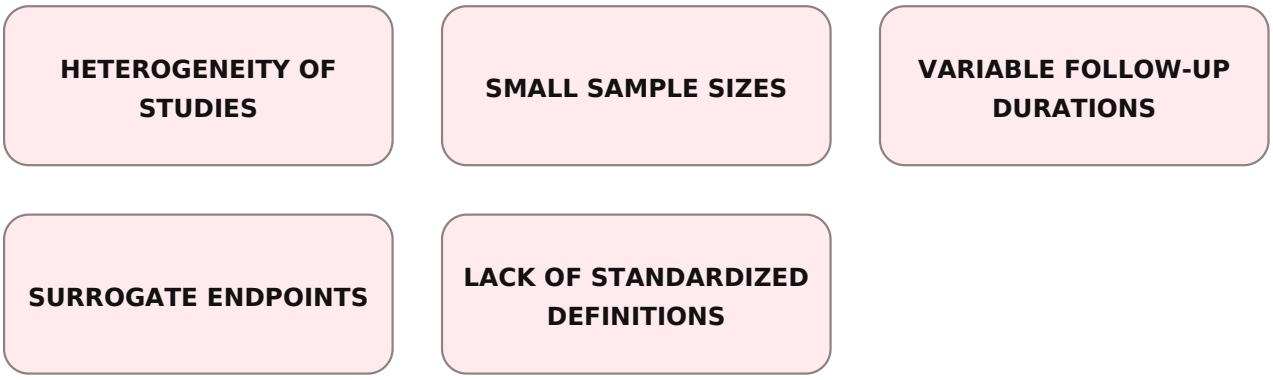


Figure 6. Future research directions (topics)