Peripheral Artery Disease and Smoking: Systematic Review with ☸SAIMSARA.

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Abstract: The aim of this paper is to comprehensively synthesize the evidence concerning the association between peripheral artery disease and smoking, including its epidemiological impact, biological mechanisms, clinical consequences, and the efficacy and challenges of smoking cessation interventions. The review utilises 232 studies with 2583291 total participants (naïve ΣN). The median odds ratio or hazard ratio for the association between current/active smoking (or genetic liability to smoking) and peripheral artery disease was 2.36, ranging from 1.301 to 4.01, unequivocally establishing smoking as a potent risk factor for PAD. While the decline in smoking-related PAD burden is observed in high-income countries, significant challenges persist in achieving widespread cessation, particularly among affected patient populations. The heterogeneity of study designs and variability in reporting metrics represent the most significant limitations to synthesizing a unified understanding. Therefore, a practical takeaway for clinicians is the critical and continuous emphasis on smoking cessation for all PAD patients, coupled with robust support mechanisms.

Keywords: Peripheral Artery Disease; Smoking; Cigarette Smoking; Smoking Cessation; Risk Factors; Atherosclerosis; Cardiovascular Disease; Disease Burden; Mortality; Inflammation

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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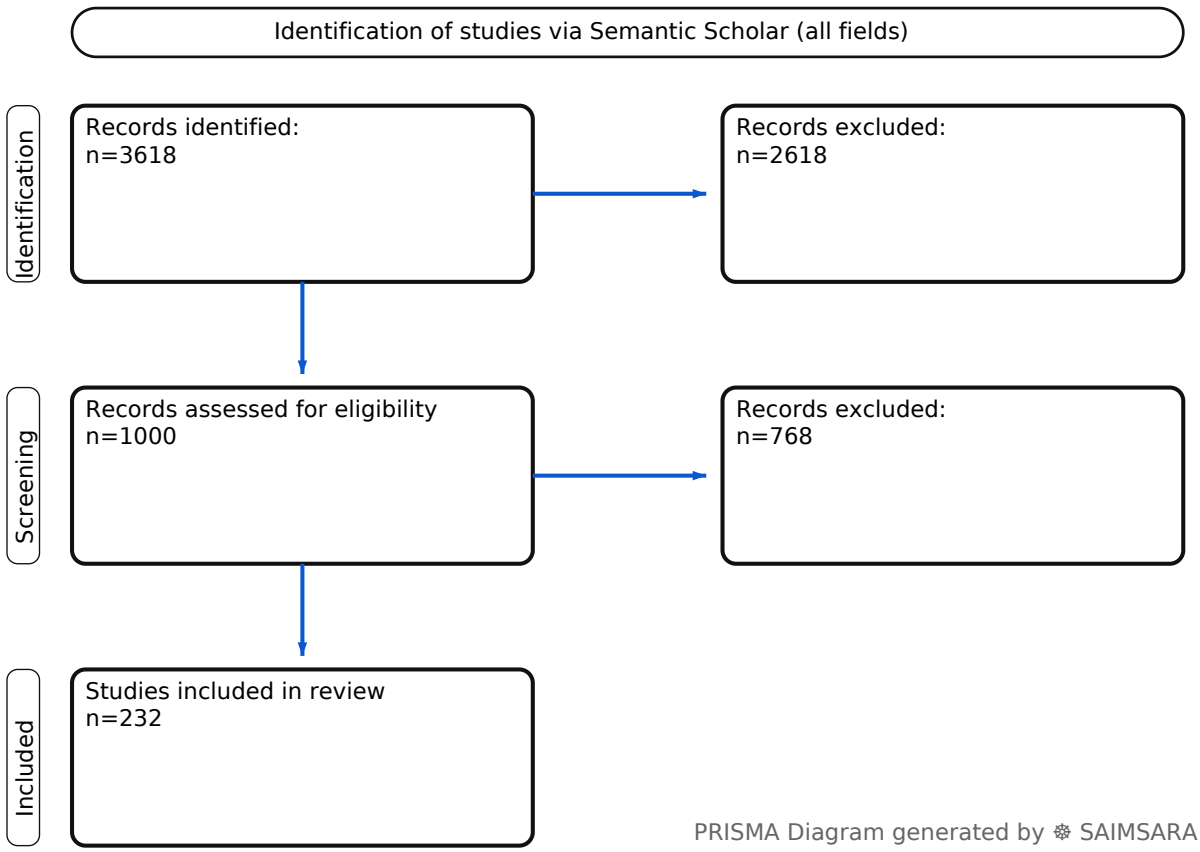
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 232
- Total study participants (naïve ΣN): 2583291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Records excluded:
n=2618
Screening
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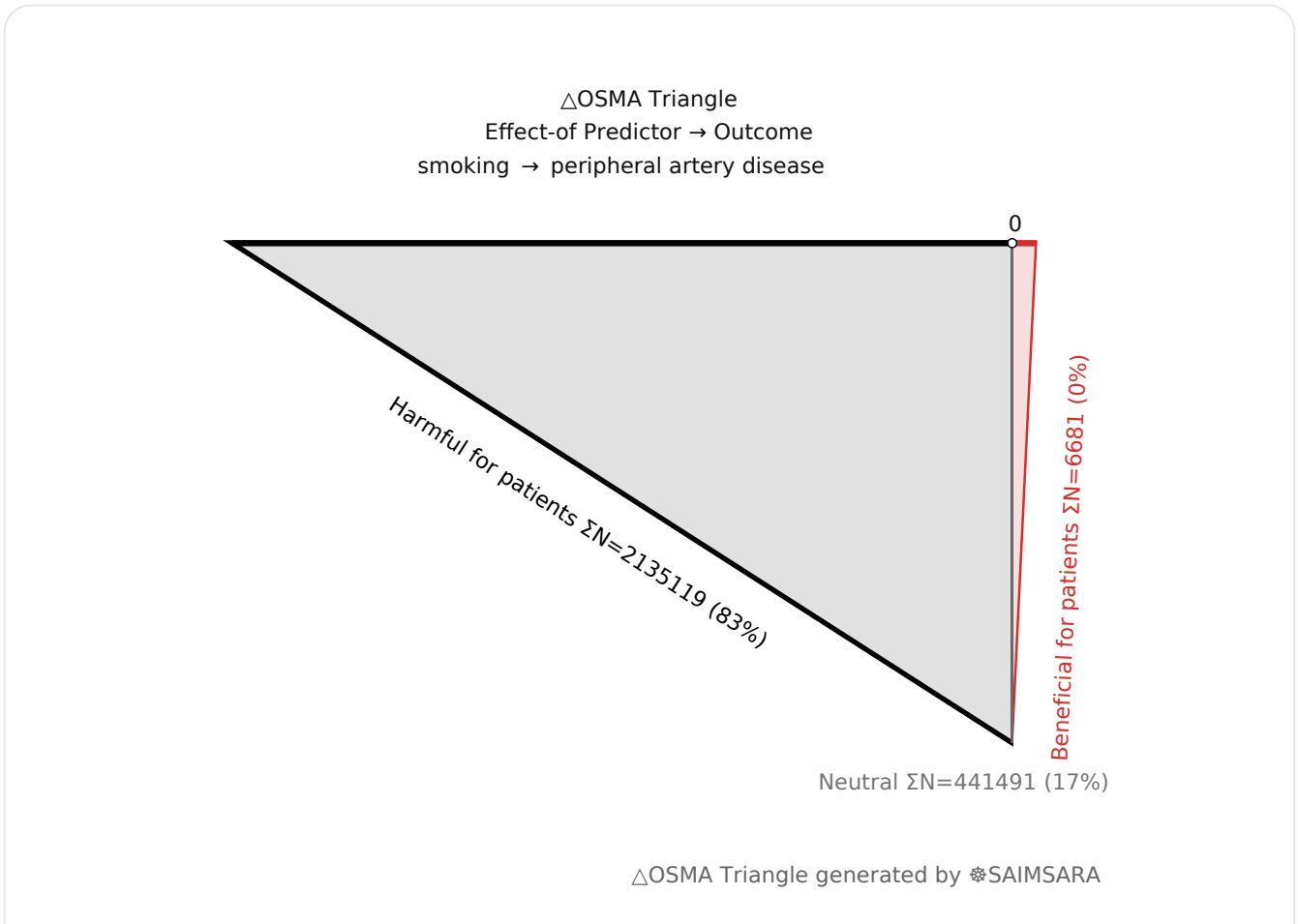
Records excluded:
n=768
Included
Studies included in review
n=232
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
smoking → peripheral artery disease
0
Harmful for patients ΣN=2135119 (83%)
Beneficial for patients ΣN=6681 (0%)
Neutral ΣN=441491 (17%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: peripheral artery disease Typical timepoints: 10-y, 12-mo. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, mortality, admission.

Predictor: smoking — exposure/predictor. Doses/units seen: 60 g. Typical comparator: high sdi countries in the past, healthy individuals, never smokers, men….

- **1) Beneficial for patients** — peripheral artery disease with smoking — [2], [12], [24], [25], [39], [109], [200], [211] — ΣN=6681
- **2) Harmful for patients** — peripheral artery disease with smoking — [1], [3], [5], [7], [8], [9], [11], [13], [14], [15], [16], [19], [20], [22], [26], [28], [30], [33], [34], [35], [37], [41], [44], [45], [46], [49], [50], [51], [52], [54], [55], [56], [59], [62], [63], [65], [66], [67], [71], [74], [75], [102], [103], [104], [105], [108], [115], [116], [118], [119], [121], [122], [123], [124], [125], [151], [152], [153], [154], [155], [157], [158], [159], [160], [161], [162], [165], [166], [167], [168], [169], [170], [172], [173], [174], [176], [178], [179], [180], [181], [183], [184], [185], [186], [188], [190], [199], [203], [204], [205], [208], [212], [215], [218], [219], [221], [223], [224], [227] — ΣN=2135119
- **3) No clear effect** — peripheral artery disease with smoking — [4], [6], [10], [17], [18], [21], [23], [27], [29], [31], [32], [36], [38], [40], [42], [43], [47], [48], [53], [57], [58], [60], [61], [64], [68], [69], [70], [72], [73], [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], [106], [107], [110], [111], [112], [113], [114], [117], [120], [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], [156], [163], [164], [171], [175], [177], [182], [187], [189], [191], [192], [193], [194], [195], [196], [197], [198], [201], [202], [206], [207], [209], [210], [213], [214], [216], [217], [220], [222], [225], [226], [228], [229], [230], [231], [232] — ΣN=441491

1) Introduction

Peripheral artery disease (PAD) represents a significant global health burden, characterized by atherosclerotic narrowing of non-coronary arteries, most commonly affecting the lower extremities. A wealth of evidence consistently identifies cigarette smoking as a primary and potent risk factor for the development and progression of PAD, exerting a profound influence on its incidence, severity, and clinical outcomes. This paper synthesizes current research on the intricate relationship between smoking and PAD, encompassing epidemiological trends, underlying biological mechanisms, clinical

implications of smoking cessation, and the challenges in managing this critical modifiable risk factor.

2) Aim

The aim of this paper is to comprehensively synthesize the evidence concerning the association between peripheral artery disease and smoking, including its epidemiological impact, biological mechanisms, clinical consequences, and the efficacy and challenges of smoking cessation interventions.

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. Randomized controlled trials (RCTs) and prospective cohort studies generally offer higher certainty regarding associations and interventions, while cross-sectional and retrospective designs are more prone to recall and selection biases. Mixed study designs often combine these approaches, with the specific components influencing overall bias. Many studies adjusted for smoking, indicating its recognized confounding role, but few focused solely on its direct causal mechanisms.

4) Results

4.1 Study characteristics:

The included studies comprised a diverse range of designs, including randomized controlled trials (RCTs) [2, 43, 75, 133, 142, 148, 211, 230, 231], prospective and retrospective cohort studies [3, 6, 7, 8, 10, 11, 14, 15, 16, 17, 19, 20, 24, 27, 28, 29, 30, 31, 33, 34, 35, 36, 38, 39, 41, 42, 46, 47, 48, 49, 50, 51, 54, 55, 58, 62, 63, 65, 66, 67, 68, 69, 71, 73, 75, 76, 77, 81, 83, 84, 86, 91, 92, 95, 96, 97, 98, 102, 103, 107, 112, 113, 117, 118, 119, 120, 121, 122, 123, 125, 128, 129, 130, 135, 137, 138, 146, 149, 150, 154, 155, 156, 157, 159, 160, 161, 162, 163, 164, 165, 167, 168, 171, 172, 173, 175, 176, 177, 178, 181, 182, 183, 184, 188, 189, 190, 193, 194, 195, 197, 200, 201, 203, 204, 208, 210, 215, 218, 222, 223, 224, 225, 228, 229], cross-sectional studies [4, 5, 9, 12, 13, 26, 32, 37, 45, 48, 49, 50, 52, 53, 59, 64, 67, 70, 72, 79, 90, 93, 101, 110, 126, 127, 133, 141, 151, 152, 153, 158, 166, 169, 180, 183, 187, 191, 192, 196, 198, 205, 213, 214, 216, 217, 220, 226, 227], and case-control studies [13, 32, 51, 53, 64, 70, 110, 170, 180, 191, 206, 227]. Populations varied widely, from general U.S. and high socio-demographic index (SDI) countries [1] to specific cohorts like Swedish men [3], individuals with type 2 diabetes [37, 55, 59, 81, 104, 115, 119, 123, 132, 137, 139, 162, 165, 166, 197, 208, 212, 226, 227, 230], Black individuals [28, 50, 73, 189], and patients undergoing various vascular procedures [14, 36, 38, 75, 96, 97, 100, 113, 114, 129, 147, 161, 196, 215, 217, 219, 224, 229]. Follow-up periods ranged from N/A for cross-sectional studies to 25 years [54], with

common durations including 9.1 years [3], 11.9 years [15], 12.6 years [20], and 31 months [1].

4.2 Main numerical result aligned to the query:

The median odds ratio (OR) or hazard ratio (HR) for the association between current/active smoking (or genetic liability to smoking) and the presence or development of peripheral artery disease was 2.36 [143], with values ranging from 1.301 [168] to 4.01 [3]. This indicates a consistently elevated risk of PAD in smokers across various populations and study designs.

4.3 Topic synthesis:

- **Smoking as a Primary Risk Factor for PAD Development:** Current smoking is consistently identified as a major, independent risk factor for PAD, contributing significantly to its development, with reported hazard ratios for current smokers reaching 4.01 (95% CI 3.17, 5.08) [3] and accounting for 45.6% (95% CI 41.1–47.2) of the risk for PAD development [7].
- **Impact of Smoking Cessation on PAD Progression and Outcomes:** Smoking cessation is associated with significant clinical improvements [24], decreased mortality, and improved amputation-free survival in PAD patients [25], and leads to a less inflammatory plasma oxylipidome profile [2].
- **Biological Mechanisms Linking Smoking to PAD:** Smoking is associated with reduced vascular reactivity and increased intima-medial thickness [62], stimulates mitochondrial biogenesis to compensate for reduced oxidative capacity [4], and is linked to changes in plasma oxylipins [2] and downregulation of miR-27b [5].
- **Epidemiology and Burden of Smoking-Related PAD:** Mortality and disease burden from smoking-related PAD declined in the U.S. and high SDI countries from 1990 to 2021, though the rate of decline in the U.S. has slowed [1]. Smoking prevalence is notably high among PAD patients, with reported rates of active smoking ranging from 30-37.3% [6, 29] to over 90% having a history of smoking [179].
- **Challenges in Smoking Cessation Among PAD Patients:** Despite the clear benefits, a significant proportion of PAD patients continue to smoke, with only 21% quitting at 3 months and 72% of active smokers continuing at 12 months [6], highlighting challenges in cessation interventions [27, 79].
- **Genetic Predispositions and Lifestyle Interactions:** Genetic liability for smoking is a strong causal risk factor for PAD [74, 185], with specific genetic variants (e.g., CHRNA4 mutation [87], nicotinic receptor cluster [76]) influencing smoking behavior and PAD risk, and unhealthy lifestyle (including smoking) increasing PAD risk even in genetically predisposed individuals [15].

- **Smoking's Role in PAD Comorbidities and Complications:** Smoking is associated with increased risk of major adverse limb events (MALE) in PAD patients [92], post-procedural complications following revascularization [75], and is a significant risk factor for diabetic foot ulcers [218] and the need for peripheral artery revascularization [14].

5) Discussion

5.1 Principal finding:

The median odds or hazard ratio for the association between current/active smoking (or genetic liability to smoking) and peripheral artery disease was 2.36 [143], ranging from 1.301 [168] to 4.01 [3], indicating that smokers face a substantially increased risk of developing or having PAD compared to non-smokers.

5.2 Clinical implications:

- **Prioritize Cessation Counseling:** Given the strong association, comprehensive, evidence-based smoking cessation interventions are critical for all PAD patients, especially those with new or worsening symptoms [6, 23, 27].
- **Early Screening for PAD in Smokers:** Individuals with a history of smoking, particularly those with other cardiovascular risk factors like diabetes, should be considered for early PAD screening to facilitate timely intervention [8, 37, 59, 159].
- **Intensified Management for Active Smokers:** Active smokers with PAD require aggressive risk factor modification and careful monitoring due to higher rates of continued smoking and increased risk of complications like major adverse limb events and post-procedural complications [6, 75, 92].
- **Address Smoking in Multimorbidity:** Smoking's impact extends to various cardiovascular and metabolic comorbidities, necessitating integrated care strategies that address smoking in the context of conditions like diabetes, coronary artery disease, and renal disease [30, 55, 104, 123].
- **Consider Genetic Susceptibility:** While not yet routine, understanding genetic predispositions to smoking and PAD may eventually allow for personalized risk assessment and targeted prevention strategies [74, 76, 87].

5.3 Research implications / key gaps:

- **Longitudinal Cessation Strategies:** Evaluate long-term efficacy and sustainability of tailored smoking cessation programs specifically for PAD patients, including behavioral and

pharmacological interventions [6, 24, 43].

- **Mechanistic Biomarker Research:** Further investigate specific molecular pathways (e.g., oxylipidome changes, microRNA expression, mitochondrial function) linking smoking to PAD pathogenesis and how these respond to cessation [2, 4, 5].
- **Personalized Intervention Strategies:** Develop and test personalized smoking cessation interventions that account for genetic predispositions, nicotine dependence levels, and psychological factors like depression, which are linked to smoking behavior [11, 79, 160].
- **Global Burden Analysis Refinement:** Conduct more granular analyses of smoking-related PAD burden and trends in diverse global populations, especially in low- and middle-income countries, to inform targeted public health interventions [1, 144].
- **Genetic-Lifestyle Interaction Studies:** Explore the interplay between specific genetic variants and lifestyle factors in modulating PAD risk in smokers, potentially identifying high-risk subgroups for intensive intervention [15, 74, 87].

5.4 Limitations:

- **Heterogeneity of Study Designs** — The diverse study designs (RCTs, cohorts, cross-sectional) limit the ability to draw uniform causal conclusions or perform comprehensive meta-analyses.
- **Variability in Reporting Metrics** — Inconsistent reporting of effect sizes (OR, HR, percentages) and statistical parameters across studies complicates direct quantitative comparison and synthesis.
- **Limited Causal Inference** — Many studies are observational, making it challenging to definitively establish causality between smoking and PAD, despite strong associations.
- **Geographic and Population Specificity** — Findings from specific populations (e.g., Swedish men, Black cohorts, specific countries) may not be fully generalizable to other diverse populations globally.
- **Incomplete Cessation Data** — While cessation benefits are noted, detailed data on the specific types, intensity, and long-term effectiveness of cessation interventions are often lacking.

5.5 Future directions:

- **RCTs for Cessation Interventions** — Conduct more randomized controlled trials evaluating novel and existing smoking cessation interventions in PAD patients.

- **Omics-Based Biomarker Discovery** — Utilize advanced omics technologies to identify novel biomarkers of smoking-induced PAD progression and response to cessation.
- **AI-Driven Risk Prediction Models** — Develop AI-driven models incorporating smoking status, genetic data, and other risk factors for personalized PAD risk prediction.
- **Implementation Science Studies** — Investigate effective strategies for implementing evidence-based smoking cessation programs in real-world clinical settings for PAD patients.
- **Comparative Effectiveness Research** — Compare the effectiveness of different smoking cessation modalities across diverse PAD patient subgroups.

6) Conclusion

The median odds ratio or hazard ratio for the association between current/active smoking (or genetic liability to smoking) and peripheral artery disease was 2.36 [143], ranging from 1.301 [168] to 4.01 [3], unequivocally establishing smoking as a potent risk factor for PAD. While the decline in smoking-related PAD burden is observed in high-income countries, significant challenges persist in achieving widespread cessation, particularly among affected patient populations. The heterogeneity of study designs and variability in reporting metrics represent the most significant limitations to synthesizing a unified understanding. Therefore, a practical takeaway for clinicians is the critical and continuous emphasis on smoking cessation for all PAD patients, coupled with robust support mechanisms.

References

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Figure 1. Publication-year distribution of included originals

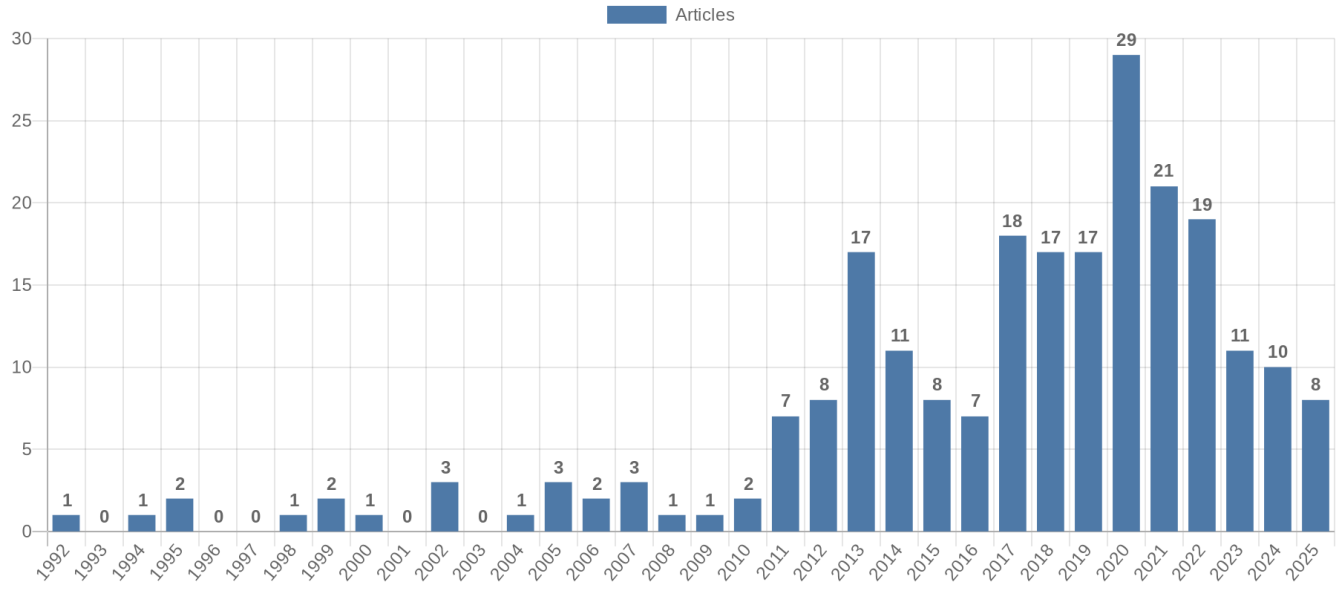

Figure 2. Study-design distribution of included originals

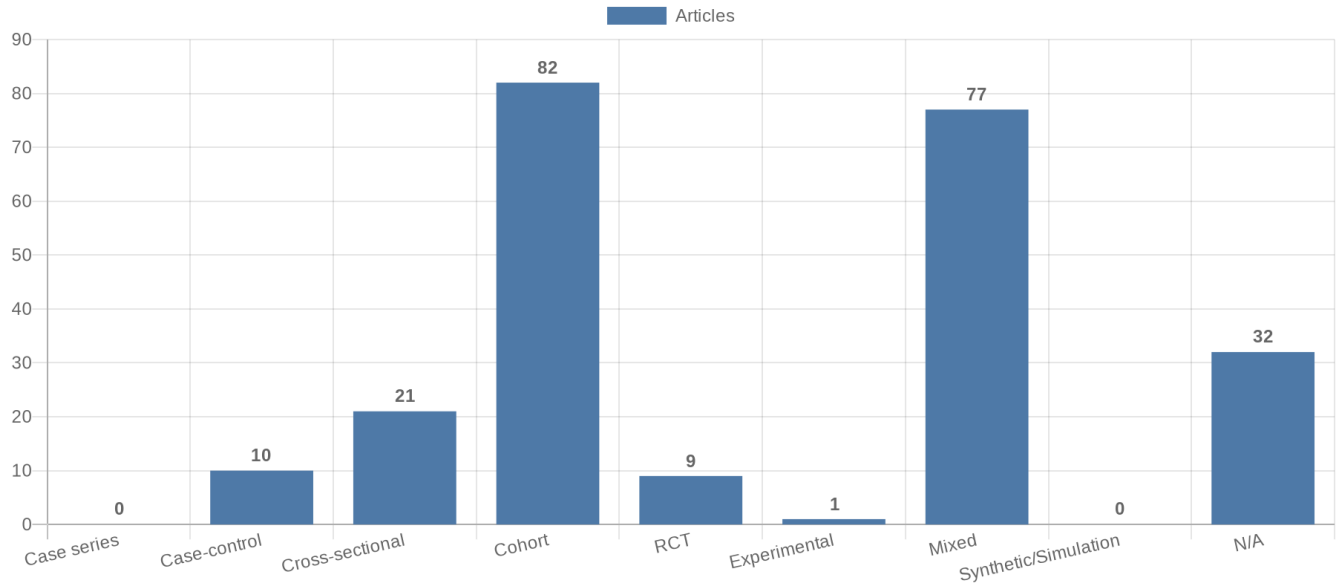

Figure 3. Study-type (directionality) distribution of included originals

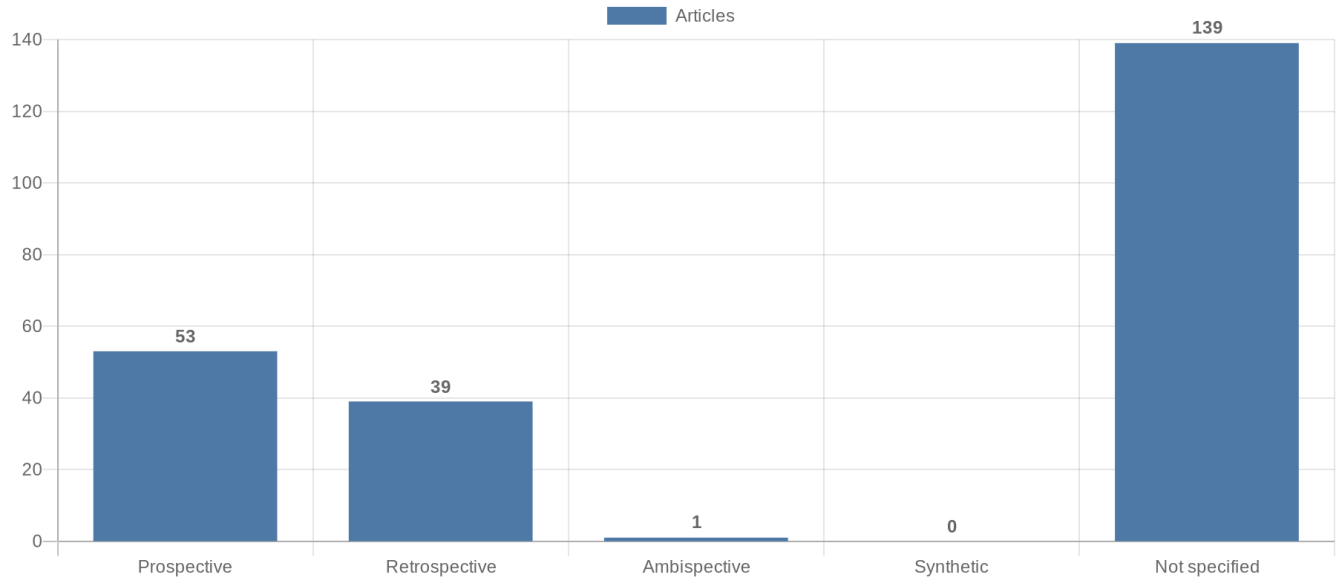

Figure 4. Main extracted research topics

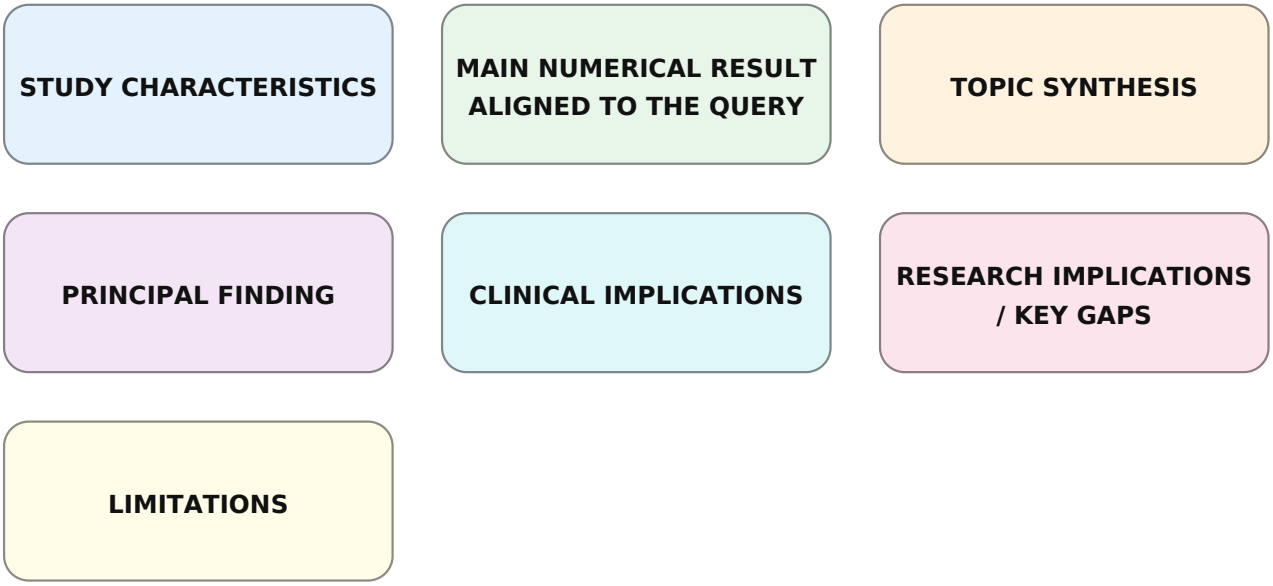

Figure 5. Limitations of current studies (topics)

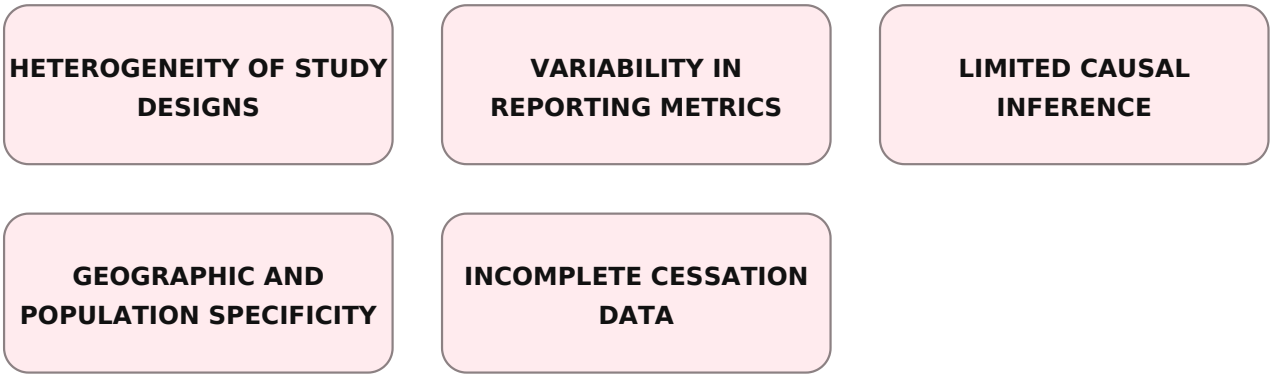

Figure 6. Future research directions (topics)