Peripheral Artery Disease and Air Pollution: Systematic Review with ☸SAIMSARA.

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Abstract: The aim of this paper is to systematically review the evidence linking air pollution exposure to peripheral artery disease, identify key pollutants and their effects, explore underlying mechanisms, and highlight areas for future research and clinical consideration. The review utilises 209 studies with 2078198 total participants (naïve ΣN). Long-term exposure to specific air pollutants is significantly associated with an increased risk of peripheral artery disease (PAD) occurrence, with hazard ratios of 1.686 (95% CI, 1.108–2.565) for sulfur dioxide and 1.200 (95% CI, 1.077–1.336) for nitrogen dioxide for a 0.01 ppm increase. These findings, supported by evidence of increased hospital admissions for PAD patients with higher PM2.5 levels, underscore air pollution as a critical, quantifiable risk factor for PAD across diverse populations. The heterogeneity in study designs and exposure metrics represents the most significant limitation affecting the certainty and generalizability of current evidence. Therefore, a concrete next step is to conduct standardized, prospective cohort studies with consistent air pollution exposure assessment and long-term follow-up to precisely quantify the impact on PAD progression and clinical outcomes.

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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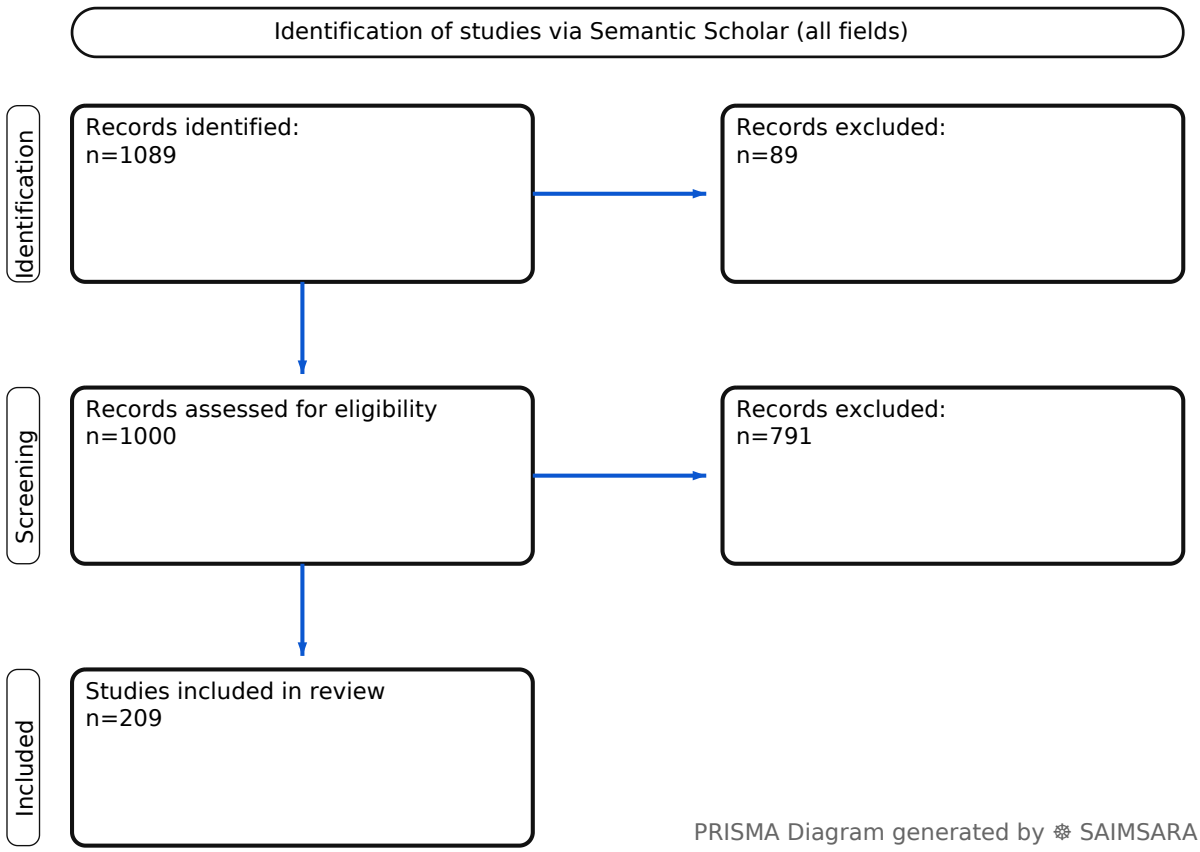
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 209
- Total study participants (naïve ΣN): 2078198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Records excluded:
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Screening
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Records excluded:
n=791
Included
Studies included in review
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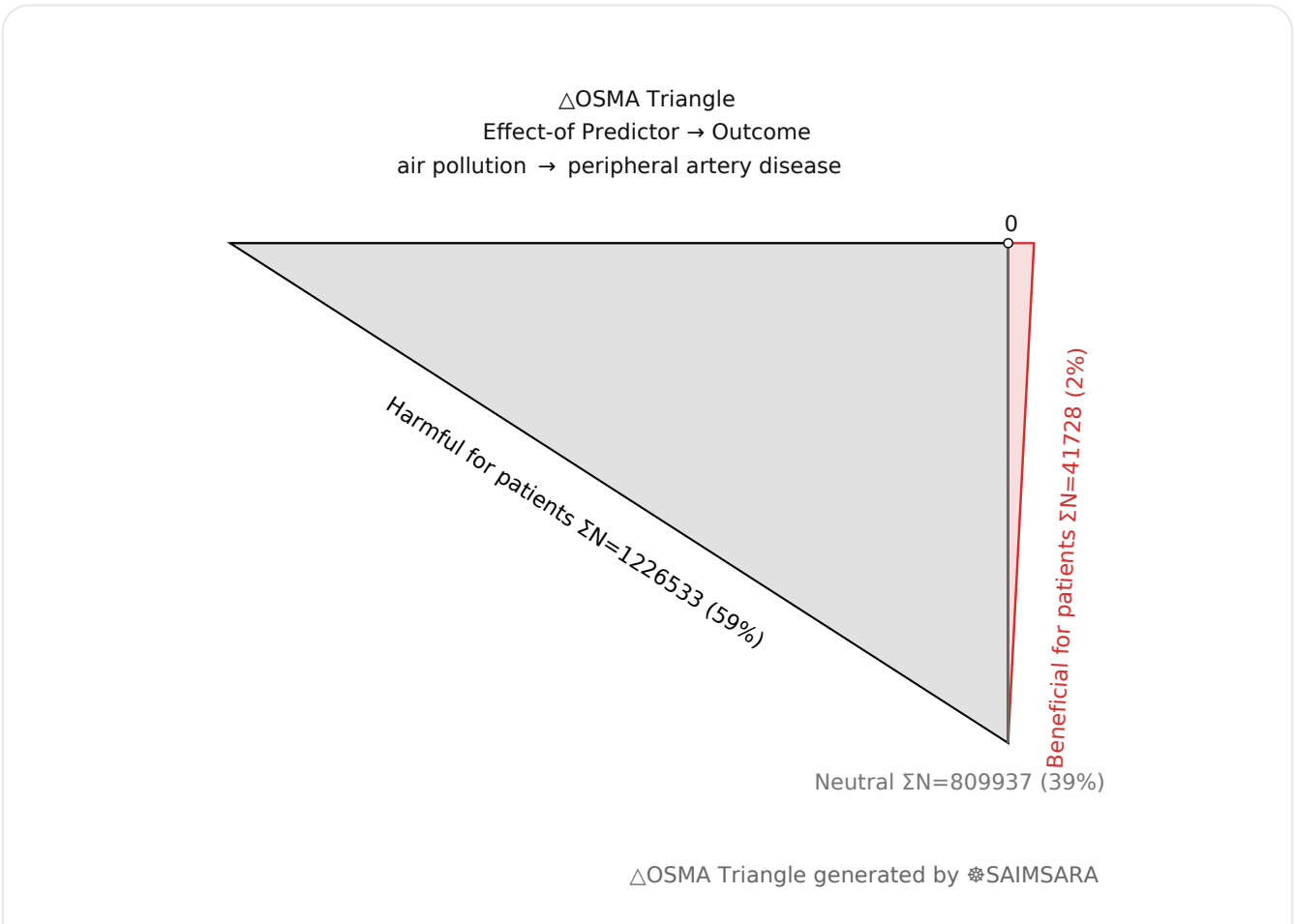
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
air pollution → peripheral artery disease
0
Harmful for patients ΣN=1226533 (59%)
Beneficial for patients ΣN=41728 (2%)
Neutral ΣN=809937 (39%)
△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: 5-y, peri/post-op. Reported metrics: %, CI, p.

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

Predictor: air pollution — exposure/predictor. Doses/units seen: 100 µg. Routes seen: intravenous. Typical comparator: ldl cholesterol, control, those without pcos, males....

- **1) Beneficial for patients** — peripheral artery disease with air pollution — [42], [59], [65], [157], [160], [163], [169] — ΣN=41728
- **2) Harmful for patients** — peripheral artery disease with air pollution — [2], [8], [13], [14], [16], [17], [18], [19], [22], [28], [30], [39], [53], [54], [55], [56], [58], [62], [63], [64], [66], [67], [68], [69], [70], [71], [72], [73], [74], [76], [78], [79], [83], [84], [86], [87], [88], [95], [98], [100], [101], [102], [103], [104], [106], [108], [110], [117], [118], [120], [121], [122], [123], [127], [128], [134], [137], [138], [140], [146], [151], [153], [155], [156], [158], [159], [161], [162], [164], [165], [167], [168], [170], [171], [174], [188], [198], [200] — ΣN=1226533
- **3) No clear effect** — peripheral artery disease with air pollution — [1], [3], [4], [5], [6], [7], [9], [10], [11], [12], [15], [20], [21], [23], [24], [25], [26], [27], [29], [31], [32], [33], [34], [35], [36], [37], [38], [40], [41], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [57], [60], [61], [75], [77], [80], [81], [82], [85], [89], [90], [91], [92], [93], [94], [96], [97], [99], [105], [107], [109], [111], [112], [113], [114], [115], [116], [119], [124], [125], [126], [129], [130], [131], [132], [133], [135], [136], [139], [141], [142], [143], [144], [145], [147], [148], [149], [150], [152], [154], [166], [172], [173], [175], [176], [177], [178], [179], [180], [181], [182], [183], [184], [185], [186], [187], [189], [190], [191], [192], [193], [194], [195], [196], [197], [199], [201], [202], [203], [204], [205], [206], [207], [208], [209] — ΣN=809937

1) Introduction

Peripheral artery disease (PAD) is a significant global health concern, characterized by the narrowing of arteries outside of the heart and brain, often leading to reduced blood flow to the limbs. Traditionally, risk factors such as smoking and diabetes mellitus have been well-established [23, 48, 41, 111]. However, a growing body of evidence suggests that environmental factors, particularly air pollution, play an increasingly critical role in the incidence, progression, and severity of cardiovascular diseases (CVDs), including PAD [1, 3, 20, 29, 37, 62, 78, 97, 123, 126, 127, 192, 198,

200]. Ambient air pollutants, such as particulate matter (PM2.5, PM10), nitrogen dioxide (NO2), sulfur dioxide (SO2), and ozone (O3), are implicated in various cardiovascular pathologies, including atherosclerosis, coronary artery disease (CAD), and myocardial infarction [11, 13, 16, 17, 18, 19, 22, 36, 38, 40, 42, 44, 45, 47, 49, 51, 53, 54, 55, 67, 70, 71, 73, 75, 77, 81, 83, 84, 86, 88, 94, 95, 98, 99, 100, 101, 104, 105, 106, 108, 109, 110, 117, 118, 119, 121, 122, 128, 130, 131, 134, 136, 139, 140, 141, 146, 149, 150, 151, 152, 153, 155, 156, 157, 158, 159, 161, 162, 166, 167, 169, 170, 174, 180, 183, 184, 188, 198, 199]. This paper aims to synthesize current research on the association between air pollution and PAD.

2) Aim

The aim of this paper is to systematically review the evidence linking air pollution exposure to peripheral artery disease, identify key pollutants and their effects, explore underlying mechanisms, and highlight areas for future research and clinical consideration.

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. Many studies were not specified for design or directionality, indicating potential for selection or reporting bias. The prevalence of mixed study designs and retrospective cohorts suggests a reliance on observational data, which can introduce confounding. Small sample sizes in some experimental and pilot studies limit generalizability.

4) Results

4.1 Study characteristics

The included studies employed a variety of designs, predominantly cohort studies, mixed methods, and cross-sectional analyses, with some randomized controlled trials (RCTs) and experimental studies. Populations ranged from large biobanks (e.g., UK Biobank, GeneBank, Korean National Health Insurance Service-National Sample Cohort) to specific patient groups (e.g., PAD patients, CAD patients, T2DM patients), healthy adults, and even animal models (mice). Follow-up periods varied widely, from short-term (hours to days) to long-term (up to 21.7 years), with many studies not specifying follow-up duration.

4.2 Main numerical result aligned to the query

Long-term exposure to specific air pollutants is significantly associated with an increased risk of peripheral artery disease (PAD). For every 0.01 ppm increase in sulfur dioxide (SO2) concentration,

the hazard ratio (HR) for PAD occurrence is 1.686 (95% CI, 1.108–2.565) [28, 39]. Similarly, for every 0.01 ppm increase in nitrogen dioxide (NO2) concentration, the HR for PAD occurrence is 1.200 (95% CI, 1.077–1.336) [28, 39]. Furthermore, an analytical model indicated that for every 10 μg/m³ increase in PM2.5 concentration, the number of hospital admissions for PAD patients increases by 0.26% [2].

4.3 Topic synthesis

- **Direct Association with PAD Incidence and Severity:** Long-term exposure to air pollution, including PM2.5, SO2, and NO2, is consistently associated with increased incidence and risk of PAD [1, 3, 5, 20, 28, 30, 39, 62, 78, 120, 123]. Elevated remnant cholesterol is also a significant risk factor for PAD [41, 43, 111].
- **Specific Pollutants and Cardiovascular Impact:** Particulate matter (PM2.5, PM10), NO2, SO2, carbon monoxide (CO), and ozone (O3) are linked to various cardiovascular outcomes. PM2.5 is associated with increased hospital admissions for PAD [2], increased coronary artery disease (CAD) risk [19] (HR 1.25, 95% CI 1.09–1.44 per 10-μg/m³ increase), myocardial infarction (MI) [86] (OR 1.63, 95% CI 1.26–2.11 for severe CAD), and adverse cardiovascular events [13] (OR 1.66, 95% CI 1.11–2.50). SO2 and NO2 significantly increase PAD occurrence [28, 39] (SO2 HR 1.686, NO2 HR 1.200 per 0.01 ppm). Long-term PM10 exposure correlates with CAD progression [16] (Spearman's rho = 0.809, $p < 0.001$) and cardiometabolic multimorbidity [45] (OR = 1.01, 95% CI 1.00–1.02 per IQR increase).
- **Genetic Susceptibility and Gene-Environment Interactions:** Genetic factors significantly modify the association between air pollution and PAD/CAD risk. A variant on chromosome 15 interacts with PM2.5 to increase CAD risk [22, 38] (OR=1.28, 95% CI 1.25-1.32 in AA homozygotes). High genetic risk combined with PM2.5 exposure is associated with increased risk of CAD, ischemic stroke, and PAD [30] (PAD HR 1.68, 95% CI 1.62-1.75). Genetic variants in the Bone Morphogenic Protein gene family modify the association between traffic exposure and PAD [96].
- **Socioeconomic and Demographic Modifiers:** Socioeconomic disadvantage and exposure bias amplify air pollution-linked PAD risk [6, 25]. Socioeconomic status also modifies the association between air pollution and symptomatic PAD [7, 26]. Sex influences the impact of air pollution, with high PM2.5 increasing obstructive CAD risk exclusively in women [14] (aOR 1.42, 95% CI 1.02-1.97) and NO2 exposure tending to increase OCAD risk primarily in female patients [122]. Older age and type 2 diabetes are also identified as risk factors for PAD [48].
- **Mechanistic Insights and Biomarkers:** Air pollution induces systemic inflammation, oxidative stress, and endothelial dysfunction [94, 104, 108, 109, 115, 118, 126, 131, 139, 146, 151, 155, 156, 157, 198, 200]. It can alter amino acid metabolism [57], deplete

mitochondrial DNA [139], and lead to carotid artery intima-media thickness (CIMT) progression [53, 70, 73, 117, 121, 140, 146]. Specific pollutants like diesel exhaust particles (DEP) cause autophagic-lysosomal blockade and abnormal cytokine expression [152].

- **PAD as a Comorbidity:** PAD is frequently identified as a comorbidity that increases mortality in patients with other cardiovascular conditions, such as those undergoing transcatheter aortic valve implantation (TAVI) [82], treated for left main coronary artery stenosis [133], or heart failure [194].
- **Mitigation and Prevention:** Filtration of traffic-related air pollution can mitigate adverse effects on blood pressure [74]. Physical activity in green environments with lower air pollution positively affects CAD patients' stress levels and hemodynamic parameters [105]. B-vitamin supplementation may attenuate DNA methylation changes and mitochondrial DNA depletion induced by PM2.5 [139].

5) Discussion

5.1 Principal finding

The principal finding of this review is that long-term exposure to air pollution, specifically sulfur dioxide (SO2) and nitrogen dioxide (NO2), significantly increases the risk of peripheral artery disease (PAD) occurrence, with hazard ratios of 1.686 (95% CI, 1.108–2.565) and 1.200 (95% CI, 1.077–1.336) respectively for a 0.01 ppm increase [28, 39]. This highlights air pollution as a critical, quantifiable risk factor for PAD.

5.2 Clinical implications

- **Risk Stratification:** Clinicians should consider long-term residential air pollution exposure as an independent risk factor when assessing patients for PAD, particularly for SO2 and NO2.
- **Patient Counseling:** Patients living in high-pollution areas, especially those with existing cardiovascular risk factors or genetic predispositions, should be counseled on the potential for increased PAD risk.
- **Environmental Interventions:** Advocacy for policies that reduce air pollution levels could be a long-term public health strategy to decrease PAD incidence and severity.
- **Monitoring and Screening:** For high-risk individuals in polluted environments, earlier or more frequent screening for subclinical atherosclerosis, such as ankle-brachial index (ABI) measurements or carotid intima-media thickness (CIMT) assessment, might be warranted.
- **Personalized Prevention:** Given the gene-environment interactions [5, 22, 30, 38, 96], future clinical approaches might involve personalized risk assessment based on both genetic profile and environmental exposure.

5.3 Research implications / key gaps

- **Standardized Exposure Metrics:** Future studies need to standardize air pollution exposure metrics (e.g., duration, concentration, specific pollutants) and their measurement methods to allow for more robust comparisons and meta-analyses.
- **Longitudinal PAD Progression:** There is a need for prospective cohort studies with long-term follow-up to precisely quantify the impact of chronic air pollution exposure on PAD progression and clinical outcomes, beyond incidence.
- **Mechanistic Pathways:** Further research is required to fully elucidate the specific molecular and cellular mechanisms by which different air pollutants contribute to PAD pathogenesis, including the role of inflammation, oxidative stress, and endothelial dysfunction.
- **Intervention Effectiveness:** Randomized controlled trials are needed to evaluate the effectiveness of air pollution mitigation strategies (e.g., air purifiers, green spaces, policy changes) on PAD incidence and progression.
- **Vulnerable Populations:** More research is needed to identify and characterize specific vulnerable populations (e.g., based on age, sex, genetic background, socioeconomic status, or comorbidities like diabetes) who are disproportionately affected by air pollution-related PAD.

5.4 Limitations

- **Study Design Heterogeneity** — The diverse range of study designs (cohort, mixed, cross-sectional, experimental) and lack of specified directionality in many studies limit the ability to draw definitive causal conclusions.
- **Inconsistent Numeric Reporting** — Varied metrics, units, and timepoints for air pollutant concentrations and health outcomes prevent comprehensive quantitative synthesis across all studies.
- **Limited Direct PAD Data** — A significant portion of the literature focuses on coronary artery disease (CAD) or general cardiovascular events, with direct PAD-specific outcomes being less numerous.
- **Confounding Factors** — Many studies do not explicitly detail adjustment for all potential confounders, such as lifestyle, diet, or other environmental exposures, which could influence the observed associations.
- **Geographic Specificity** — Studies are conducted in various global settings, and findings may not be fully generalizable due to differences in pollutant composition, environmental regulations, and population characteristics.

5.5 Future directions

- **Standardize Exposure Assessment** — Develop and implement standardized methods for assessing individual and population-level air pollution exposure, including personal monitoring.
- **Multi-Omics Research** — Conduct multi-omics studies (genomics, epigenomics, metabolomics) to identify novel biomarkers and pathways linking air pollution to PAD.
- **Intervention Trials** — Design and execute randomized controlled trials to evaluate the efficacy of air quality interventions on PAD prevention and management.
- **Global Burden Studies** — Perform comprehensive global burden of disease studies specifically focused on the attributable risk of PAD due to various air pollutants.
- **Policy Impact Analysis** — Evaluate the long-term impact of air quality policies and regulations on PAD incidence and prevalence in diverse populations.

6) Conclusion

Long-term exposure to specific air pollutants is significantly associated with an increased risk of peripheral artery disease (PAD) occurrence, with hazard ratios of 1.686 (95% CI, 1.108–2.565) for sulfur dioxide and 1.200 (95% CI, 1.077–1.336) for nitrogen dioxide for a 0.01 ppm increase [28, 39]. These findings, supported by evidence of increased hospital admissions for PAD patients with higher PM2.5 levels [2], underscore air pollution as a critical, quantifiable risk factor for PAD across diverse populations. The heterogeneity in study designs and exposure metrics represents the most significant limitation affecting the certainty and generalizability of current evidence. Therefore, a concrete next step is to conduct standardized, prospective cohort studies with consistent air pollution exposure assessment and long-term follow-up to precisely quantify the impact on PAD progression and clinical outcomes.

References

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Figure 1. Publication-year distribution of included originals

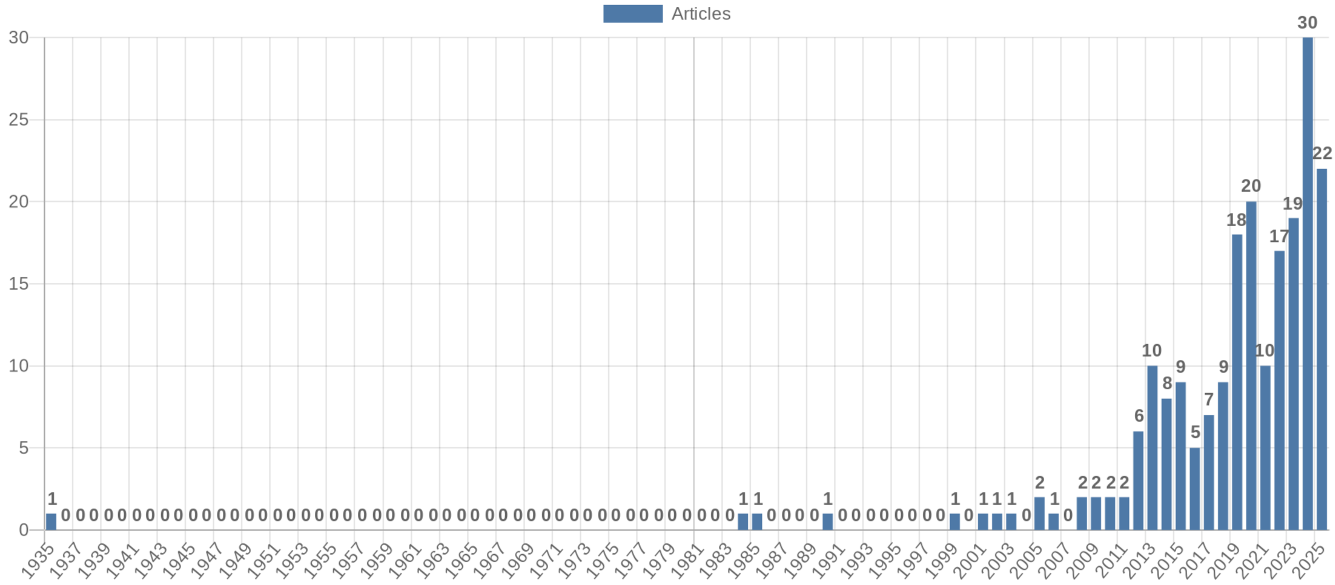

Figure 2. Study-design distribution of included originals

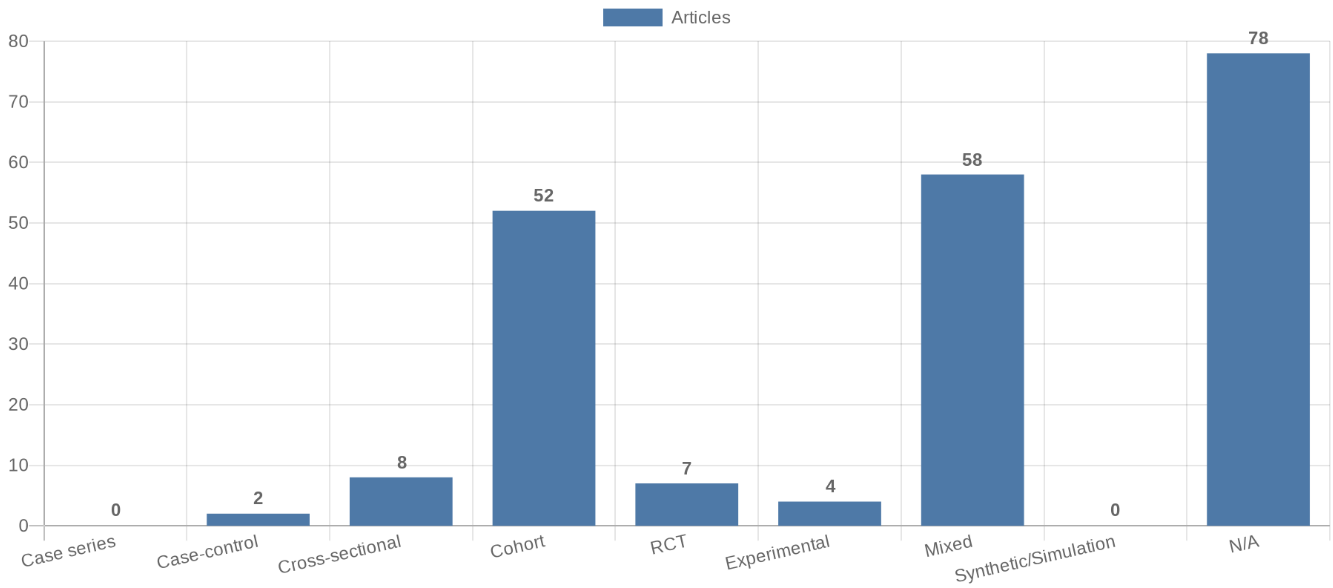

Figure 3. Study-type (directionality) distribution of included originals

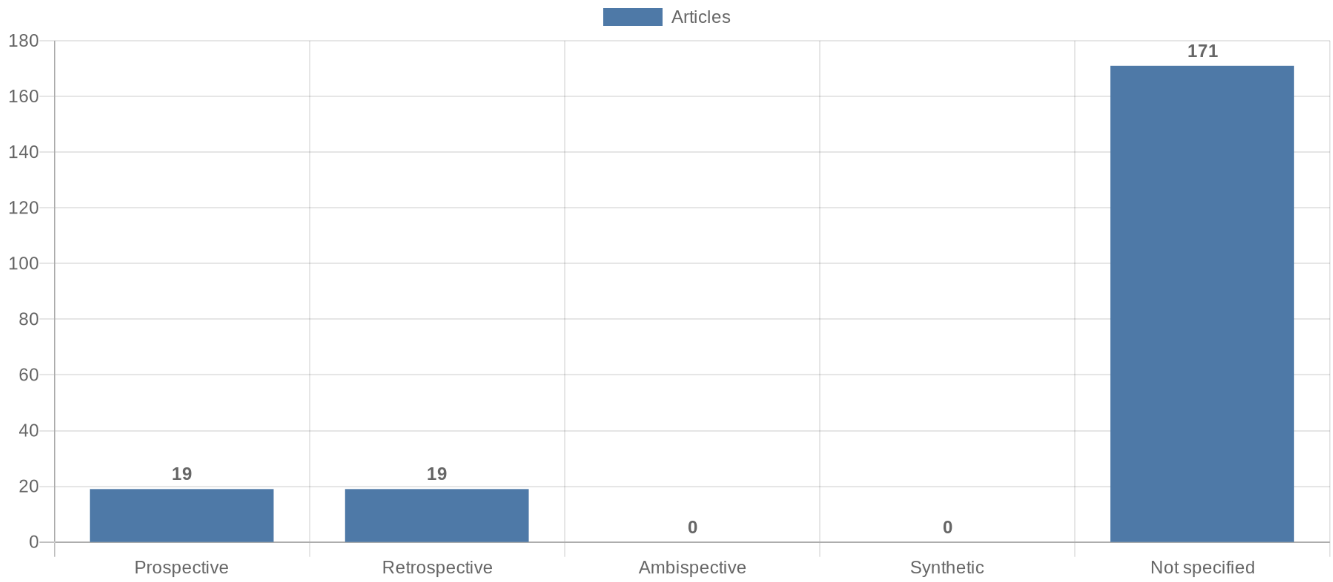

Figure 4. Main extracted research topics

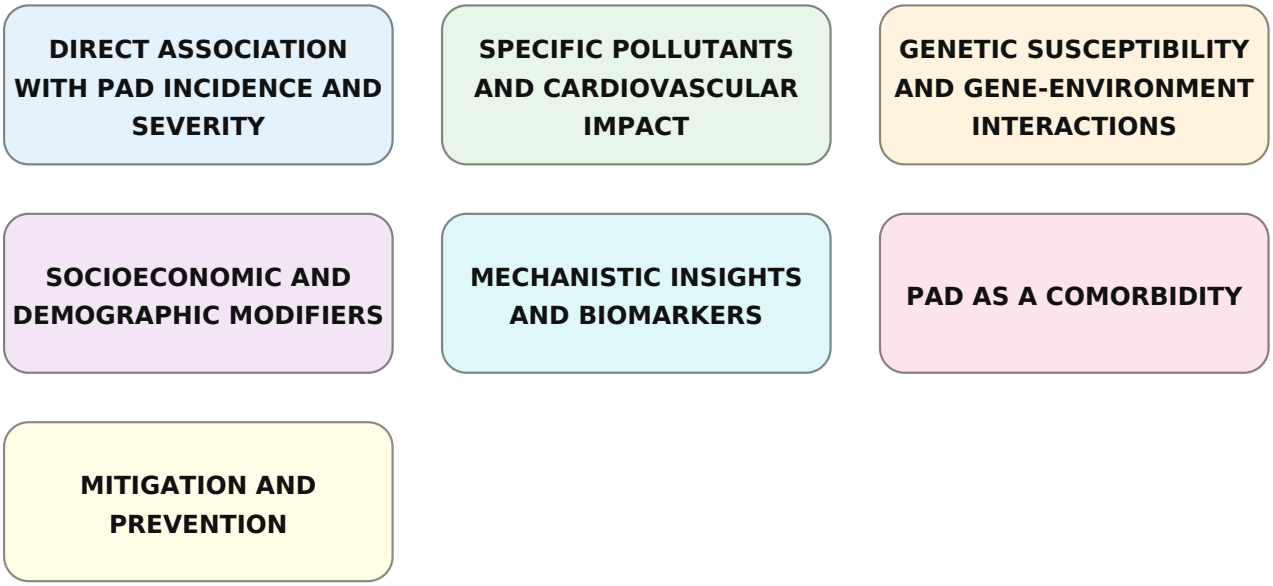

Figure 5. Limitations of current studies (topics)

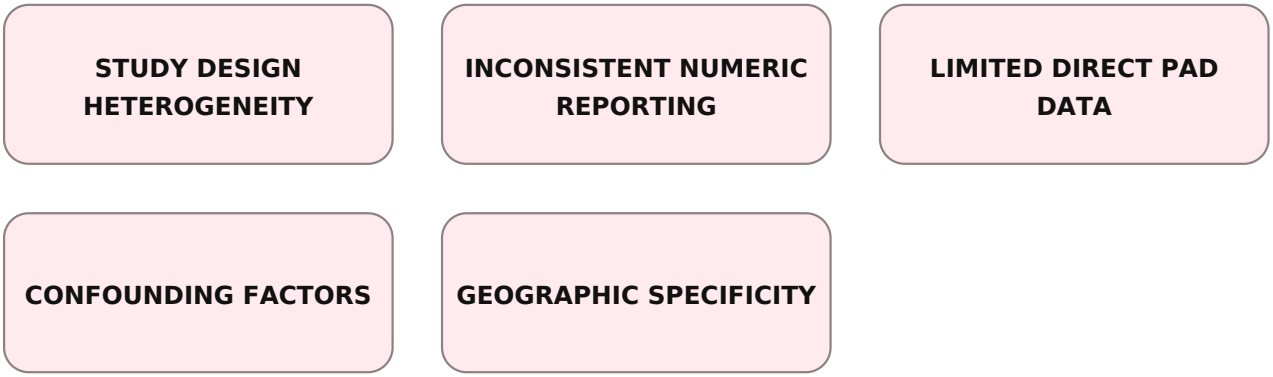

Figure 6. Future research directions (topics)