Peripheral Artery Disease Pathophysiology: Systematic Review with ☸SAIMSARA.

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Abstract: This paper aims to synthesize current understanding of the pathophysiology of peripheral artery disease by systematically extracting and integrating findings from recent research, highlighting key molecular and cellular mechanisms, contributing risk factors, and their clinical implications. The review utilises 183 studies with 1018071 total participants (naïve ΣN). The median observed risk association for peripheral artery disease (PAD) or its related outcomes, reported as odds ratios (OR) or hazard ratios (HR), was 1.41, with a range from 1.17 to 2.06. This underscores the significant impact of various pathological mechanisms on PAD development and adverse outcomes across diverse patient populations. The heterogeneity of study designs and reporting, however, represents a significant limitation to the certainty of these findings. Clinicians should prioritize comprehensive risk factor management and consider the systemic nature of PAD, while future research should focus on validating specific biomarkers and developing targeted therapies for mitochondrial dysfunction.

Keywords: ["Peripheral Artery Disease; Atherosclerosis; Inflammation; Thrombosis; Vascular Dysfunction; Mitochondrial

Review Stats

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- Scope: All fields
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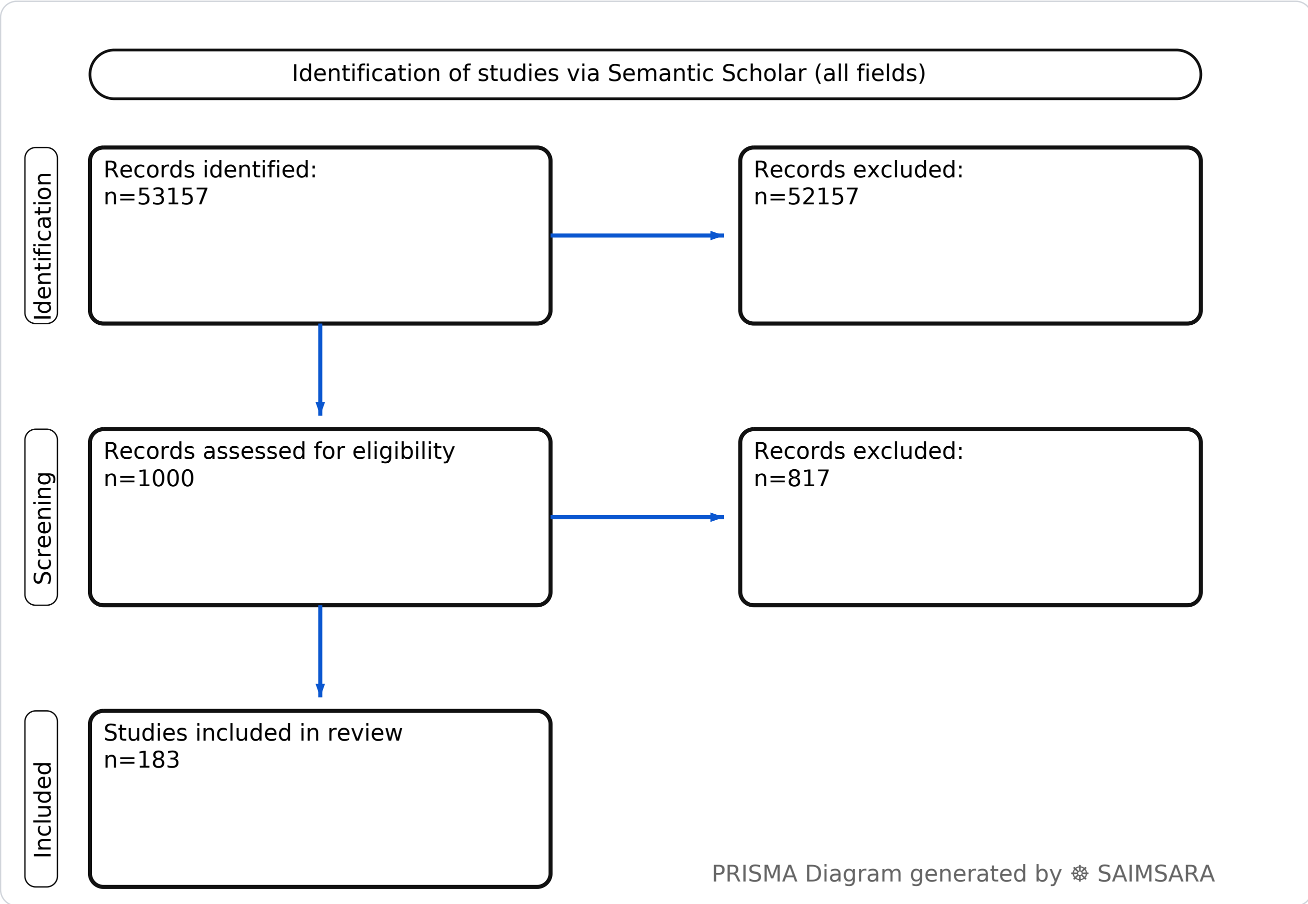
- Included original Abstracts/Papers: 183
- Total study participants (naïve ΣN): 1018071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Records excluded:
n=52157
Screening
Records assessed for eligibility
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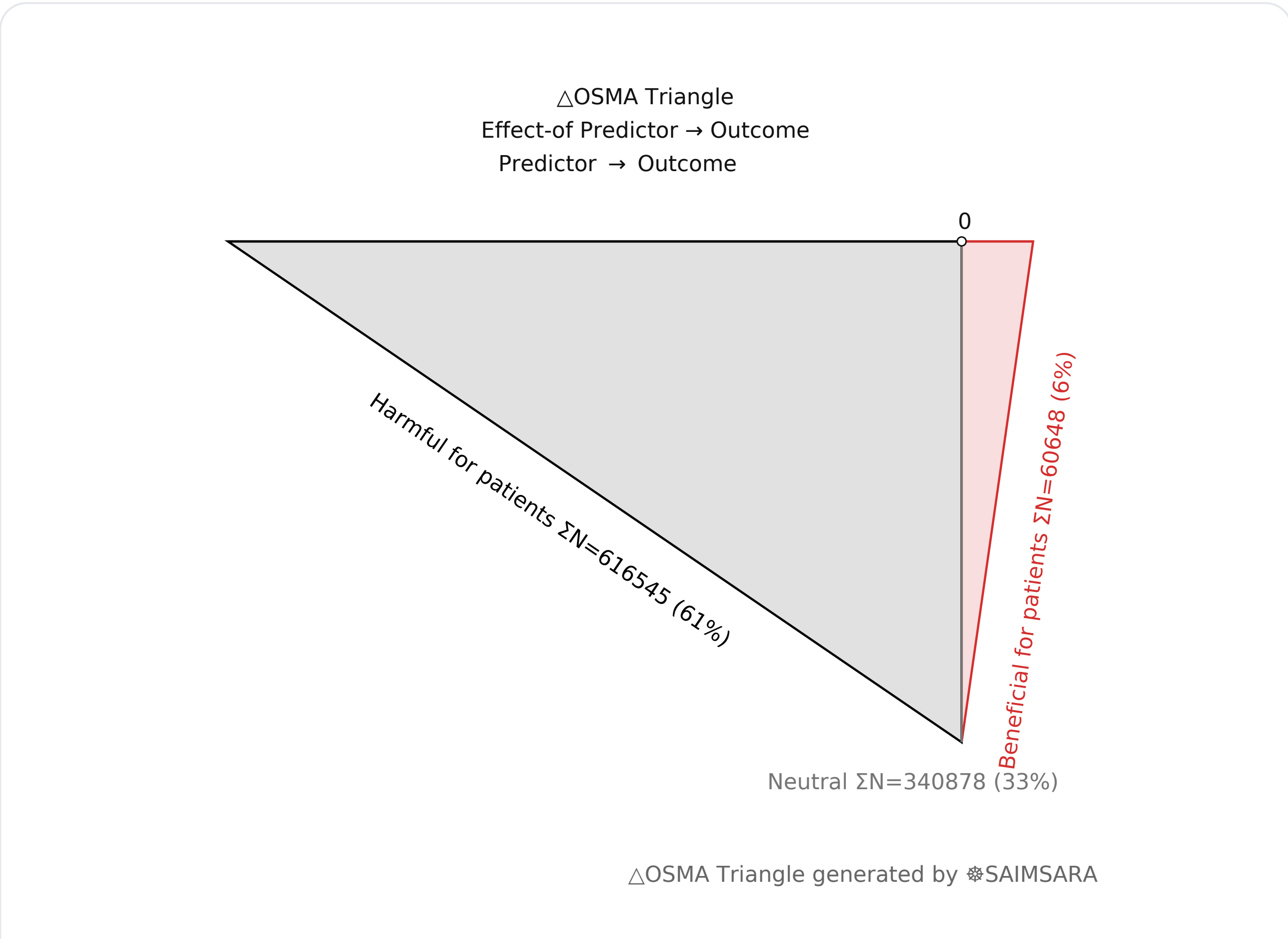
Records excluded:
n=817
Included
Studies included in review
n=183
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
Predictor → Outcome
0
Harmful for patients ΣN=616545 (61%)
Beneficial for patients ΣN=60648 (6%)
Neutral ΣN=340878 (33%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: Outcome Typical timepoints: peri/post-op, 30-day. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, mortality, functional.

Predictor: Predictor — exposure/predictor. Typical comparator: coronary atherosclerosis, those without vascular disease, control, those without pad….

- **1) Beneficial for patients** — Outcome with Predictor — [16], [24], [39], [44], [77], [79], [82], [85], [90], [92], [94], [106], [110], [118], [135], [141], [177], [182] — ΣN=60648
- **2) Harmful for patients** — Outcome with Predictor — [1], [3], [4], [5], [6], [7], [9], [10], [11], [12], [13], [14], [15], [17], [18], [19], [21], [22], [25], [33], [37], [51], [54], [55], [56], [60], [65], [66], [67], [68], [69], [71], [72], [73], [75], [81], [83], [84], [86], [87], [91], [95], [96], [98], [99], [104], [107], [108], [111], [112], [114], [126], [128], [129], [133], [134], [136], [137], [138], [139], [142], [144], [148], [149], [153], [155], [156], [158], [159], [161], [162], [163], [166], [168], [169], [174], [175], [178], [179], [180], [181], [183] — ΣN=616545
- **3) No clear effect** — Outcome with Predictor — [2], [8], [20], [23], [26], [27], [28], [29], [30], [31], [32], [34], [35], [36], [38], [40], [41], [42], [43], [45], [46], [47], [48], [49], [50], [52], [53], [57], [58], [59], [61], [62], [63], [64], [70], [74], [76], [78], [80], [88], [89], [93], [97], [100], [101], [102], [103], [105], [109], [113], [115], [116], [117], [119], [120], [121], [122], [123], [124], [125], [127], [130], [131], [132], [140], [143], [145], [146], [147], [150], [151], [152], [154], [157], [160], [164], [165], [167], [170], [171], [172], [173], [176] — ΣN=340878

1) Introduction

Peripheral artery disease (PAD) is a prevalent atherosclerotic condition affecting arteries outside of the heart and brain, leading to reduced blood flow, particularly in the lower extremities. Its pathophysiology is complex and multifactorial, involving a cascade of inflammatory, metabolic, and cellular processes that contribute to vascular dysfunction, arterial remodeling, and tissue ischemia [1, 7, 15, 25, 38]. Understanding these intricate mechanisms is crucial for effective prevention, diagnosis, and treatment strategies, especially given PAD's significant association with other cardiovascular diseases (CVD) and adverse outcomes [18, 21, 25, 71, 133].

2) Aim

This paper aims to synthesize current understanding of the pathophysiology of peripheral artery disease by systematically extracting and integrating findings from recent research, highlighting key molecular and cellular mechanisms, contributing risk factors, and their clinical implications.

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 comprise a mix of review articles, cohort studies, cross-sectional analyses, randomized controlled trials (RCTs), case-control studies, case series, and experimental models. Many studies did not specify a design or directionality, and several were review articles, which can introduce synthesis bias. Sample sizes varied widely, from single case reports to large cohorts of over 200,000 participants, impacting generalizability. The lack of consistent reporting for statistics and follow-up in many summaries further limits a quantitative assessment of bias.

4) Results

4.1 Study characteristics

The included studies featured a diverse range of designs, including mixed methods, cohort studies, cross-sectional analyses, randomized controlled trials, case-control studies, case series, and experimental models, with many studies not explicitly specifying a design. Populations varied from patients with PAD, specific comorbidities like chronic kidney disease (CKD) or diabetes, and coronary artery disease (CAD), to healthy controls and animal models (mice, pigs, rats). Follow-up periods, when reported, ranged from 30 days to 17.4 years, with many studies not specifying a follow-up duration.

4.2 Main numerical result aligned to the query

The median observed risk association for peripheral artery disease (PAD) or its related outcomes, reported as odds ratios (OR) or hazard ratios (HR), was 1.41, with a range from 1.17 to 2.06. Specifically, the triglyceride-glucose index (TyGI) showed an OR of 1.92 (95% CI: 1.50–2.45) for association with PAD [13], while smoking was associated with a HR of 2.06 (95% CI, 1.88-2.26) for incident PAD in men [98]. Galectin-3 and hs-CRP were independently associated with incident PAD, with adjusted HRs of 1.17 (95% CI, 1.05–1.31) and 1.25 (95% CI, 1.05–1.49) respectively [69]. Depressive symptoms were associated with a greater risk of PAD (OR = 1.79, 95% CI = 1.06–3.04) [99], and β2-microglobulin was associated with an increased risk of symptomatic PAD (RR 1.41, 95% CI 1.10 to 1.81) in pooled analyses [96].

4.3 Topic synthesis

- **Inflammation and Immune Dysregulation:** Inflammation is central to atherosclerosis development and progression in PAD, impacting endothelial barrier function, promoting pro-coagulability, and leading to vascular remodeling and reduced tissue perfusion due to fibrosis [1]. Monocyte phenotypic plasticity is crucial in atherogenesis, plaque progression, ischemia-reperfusion injury, and chronic ischemic remodeling [3]. Inflammatory burden varies by anatomical location, with below-the-knee (BTK) lesions exhibiting greater systemic inflammation, and inflammatory indices like NLR, SII, and SIRI can predict endovascular treatment outcomes [10, 39, 104]. Genetic and transcriptome-wide analyses confirm inflammatory signaling's contribution to atherosclerosis and vascular dysfunction [11, 15]. Elevated levels of IL-6 are significantly associated with PAD [129], and osteopontin (OPN) influences macrophage activation, monocyte infiltration, and vascular smooth muscle cell activity in atherosclerosis [122].
- **Oxidative Stress and Mitochondrial Dysfunction:** Oxidative stress plays a significant role in PAD pathophysiology, contributing to endothelial dysfunction, arterial stiffness, and inflammation, often linked to NADPH oxidase 2 (NOX2)-derived reactive oxygen species and decreased nitric oxide (NO) bioavailability [22, 26, 113]. The NO system is compromised in PAD, with dysregulation worsening as the disease progresses [19]. Skeletal muscle mitochondrial dysfunction is a key component of PAD myopathy, characterized by reduced oxygen consumption, increased hydrogen peroxide production, and accumulation of electron transport chain complexes due to impaired mitophagy in ischemic conditions [27, 59, 62, 64, 75, 78, 81]. Cocoa flavanols may enhance antioxidant capacity via Nrf2 activation, improving muscle function [16].
- **Metabolic Dysregulation and Lipid Metabolism:** Lipids play a significant role in incident PAD and adverse outcomes, with lipid-modifying therapies being important for prevention [12]. The triglyceride-glucose index (TyGI) is associated with PAD, suggesting a role for insulin resistance [13]. Diabetes mellitus is a major risk factor, promoting atherosclerosis and plaque instability through altered metabolism, endothelial dysfunction, and arterial stiffness [29, 54, 60, 117]. Patients with claudication are insulin resistant and have reduced calf muscle glucose uptake [37]. Serum metabolomics reveals distinct metabolic signatures associated with PAD progression, differentiating chronic limb-threatening ischemia (CLTI) from intermittent claudication (IC) [20, 23, 28]. The plasma oxylipidome is implicated, with smoking cessation leading to a less inflammatory profile [74].
- **Thrombosis and Coagulation:** Thrombosis is a key manifestation in PAD, with etiologies differing from coronary atherosclerosis, and cardiovascular mortality is higher in PAD without myocardial infarction/stroke [5]. Atherosclerosis disrupts vascular homeostasis, triggering pro-thrombotic responses through platelet activation, aggregation, and vasoconstriction,

leading to lumen restriction or occlusion [14]. Antiplatelet therapies like vorapaxar can reduce thrombotic cardiovascular events in PAD patients [140].

- **Vascular Remodeling and Calcification:** Atherosclerosis leads to vascular remodeling, affecting endothelial barrier properties, promoting fibrosis, and causing reduced tissue perfusion [1]. Smoking induces endothelial cell dysfunction, smooth muscle cell remodeling, and macrophage phenotypic transformation [6]. Angioscopy reveals varying plaque components in stenosis and occlusion [33]. Arterial stiffness, reflected by brachial-ankle pulse wave velocity (baPWV), is associated with cardiovascular risk factors [139]. Vascular calcification, particularly medial calcification, is promoted by altered mineral metabolism in chronic kidney disease (CKD) and strongly associated with PAD [35, 58, 153]. 18F-NaF PET/CT imaging can detect and predict calcium progression in PAD [66].
- **Genetic and Environmental Factors:** Genetic and environmental factors are crucial in PAD pathophysiology, with specific genetic variants associated with plaque initiation, progression, and rupture [15]. Genome-wide association studies have identified new genetic loci for PAD, highlighting similarities and differences with coronary and cerebral atherosclerosis [76]. Smoking is a major preventable factor [6, 98], and traffic exposure interacts with genetic variants in the Bone Morphogenic Protein (BMP) gene family to modify PAD risk [105]. Exposure to contaminant metals like lead, cadmium, and arsenic has been linked to PAD through oxidative stress and inflammation [113].
- **Comorbidities and Systemic Associations:** PAD often coexists with other cardiovascular conditions; 18% of patients with CAD also have PAD [21]. Chronic kidney disease (CKD) significantly exacerbates ischemic muscle pathology in PAD, diminishing muscle strength and mitochondrial function [4, 17, 35]. Diabetes is a strong risk factor for PAD and its progression, particularly chronic limb-threatening ischemia (CLTI) [29, 57]. Sex-based disparities exist in PAD epidemiology, pathophysiology, risk factors, and treatment outcomes, with females often experiencing underdiagnosis and undertreatment [8, 9, 95]. Microvascular disease independently and synergistically increases the risk of amputation in PAD patients [72]. Depression is associated with a greater risk of PAD [99].

5) Discussion

5.1 Principal finding

The synthesis of current research indicates that risk factors for peripheral artery disease (PAD) or its progression are associated with a median increased risk of 1.41 (ranging from 1.17 to 2.06), emphasizing the significant impact of various pathological mechanisms on disease development and adverse outcomes [13, 69, 96, 98, 99].

5.2 Clinical implications

- **Comprehensive Risk Factor Management:** Given the strong associations of smoking [98], diabetes [29, 54], insulin resistance [13, 37], and dyslipidemia [12] with PAD, aggressive management of these modifiable risk factors is critical for prevention and disease control.
- **Inflammation as a Diagnostic/Prognostic Tool:** Inflammatory markers like NLR, SII, SIRI, hs-CRP, and galectin-3 can predict PAD progression and treatment outcomes, suggesting their utility in risk stratification and monitoring, especially for below-the-knee lesions [10, 39, 69, 104].
- **Recognition of Systemic Disease:** PAD is often a manifestation of systemic atherosclerosis, frequently coexisting with CAD and CVD [21, 25]. Clinicians should screen for PAD in patients with other atherosclerotic diseases and vice versa, recognizing the higher cardiovascular mortality in PAD patients even without MI/stroke [5, 18].
- **Addressing Comorbidities:** Chronic kidney disease significantly worsens PAD-associated myopathy and mitochondrial function [4, 17, 35], necessitating integrated care for these high-risk patients.
- **Sex-Specific Considerations:** Awareness of sex-based disparities in PAD epidemiology, presentation, and outcomes is essential to combat underdiagnosis and undertreatment in females [8, 9, 95].

5.3 Research implications / key gaps

- **Biomarker Validation in Diverse Cohorts:** Further studies are needed to validate the diagnostic and prognostic utility of identified biomarkers (e.g., specific metabolomic profiles, inflammatory indices, genetic variants) across diverse populations and PAD stages, including their utility in predicting therapeutic response [2, 20, 23, 28].
- **Mechanistic Link between Comorbidities and PAD:** Research should further elucidate the precise molecular mechanisms by which comorbidities like CKD, diabetes, and microvascular disease exacerbate PAD pathophysiology, particularly focusing on their impact on muscle pathology and mitochondrial function [4, 17, 35, 72].
- **Targeting Mitochondrial Dysfunction:** Given the consistent implication of mitochondrial dysfunction and oxidative stress in PAD myopathy, future research should explore targeted therapies, such as Nrf2 activators or interventions to improve mitophagy, to enhance muscle function and tissue perfusion [16, 27, 59, 62, 75, 78, 81].
- **Sex-Specific Mechanistic Studies:** More research is required to understand the underlying sex-specific pathophysiological differences in PAD, including endothelial cell mitochondrial dysfunction in females with diabetes-associated PAD, to develop tailored interventions [8, 9, 95].

- **Longitudinal Multi-Omics Integration:** Integrating genetic, transcriptomic, proteomic, and metabolomic data longitudinally could provide a more comprehensive understanding of PAD initiation and progression, identifying novel pathways and therapeutic targets [11, 15, 20, 23, 70, 76].

5.4 Limitations

- **Study Design Heterogeneity** — The varied study designs, including reviews, observational studies, and experimental models, limit direct comparison and meta-analysis of findings.
- **Inconsistent Reporting of Statistics** — Many summaries lacked detailed statistical reporting (e.g., full CIs, p-values for all findings), hindering a quantitative synthesis of effects.
- **Qualitative Bias Assessment** — Bias was qualitatively inferred due to the nature of the structured summary, precluding a formal, quantitative bias assessment.
- **Limited Long-Term Follow-up** — While some studies had long follow-up, many did not specify, potentially limiting insights into long-term disease progression and treatment efficacy.
- **Population Specificity** — Some studies focused on specific patient cohorts (e.g., vascular surgery inpatients, CAD patients), which may limit the generalizability of findings to the broader PAD population.

5.5 Future directions

- **Biomarker Panel Development** — Develop and validate comprehensive biomarker panels that integrate inflammatory, metabolic, and genetic markers for early PAD detection and risk stratification.
- **Mitochondrial Therapy Trials** — Conduct randomized controlled trials evaluating interventions targeting mitochondrial dysfunction and oxidative stress in PAD patients to improve muscle function and limb outcomes.
- **Gender-Specific Research** — Prioritize research specifically designed to investigate sex-based differences in PAD pathophysiology and treatment responses to develop tailored therapies.
- **AI-Driven Predictive Models** — Utilize machine learning to integrate diverse clinical, genetic, and omics data to build robust predictive models for PAD progression and treatment outcomes.

- **Environmental Factor Impact** — Investigate the precise mechanisms by which environmental factors, such as air pollution and heavy metal exposure, contribute to PAD development and progression.

6) Conclusion

The median observed risk association for peripheral artery disease (PAD) or its related outcomes, reported as odds ratios (OR) or hazard ratios (HR), was 1.41, with a range from 1.17 to 2.06 [13, 69, 96, 98, 99]. This underscores the significant impact of various pathological mechanisms on PAD development and adverse outcomes across diverse patient populations. The heterogeneity of study designs and reporting, however, represents a significant limitation to the certainty of these findings. Clinicians should prioritize comprehensive risk factor management and consider the systemic nature of PAD, while future research should focus on validating specific biomarkers and developing targeted therapies for mitochondrial dysfunction.

References

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Figure 1. Publication-year distribution of included originals

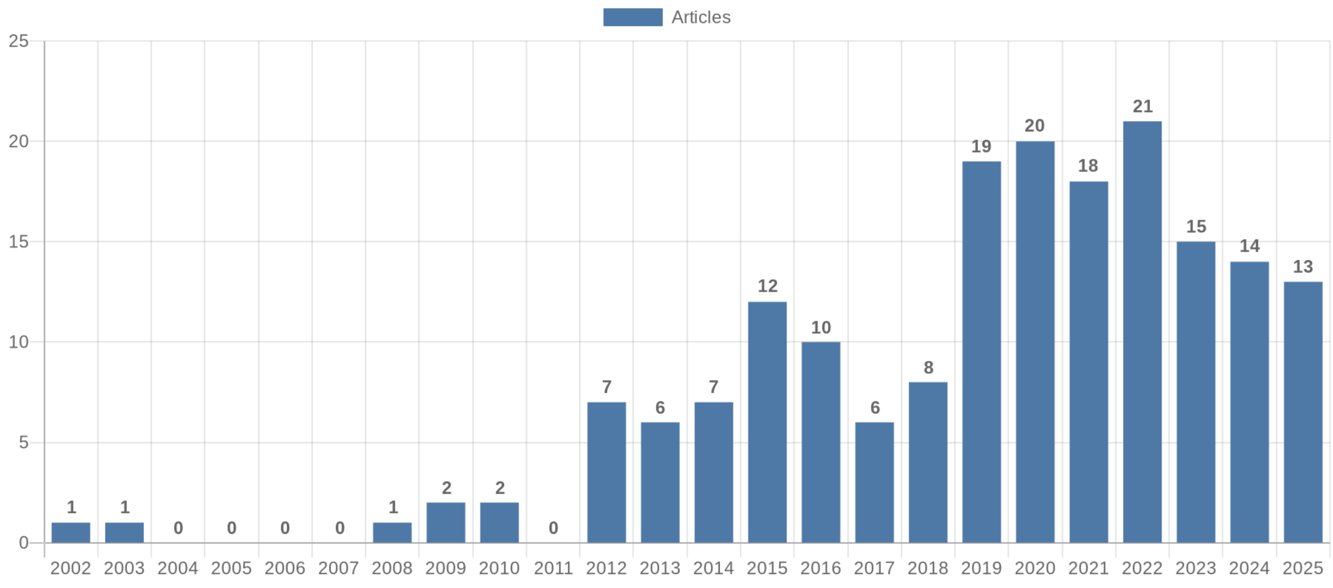

Figure 2. Study-design distribution of included originals

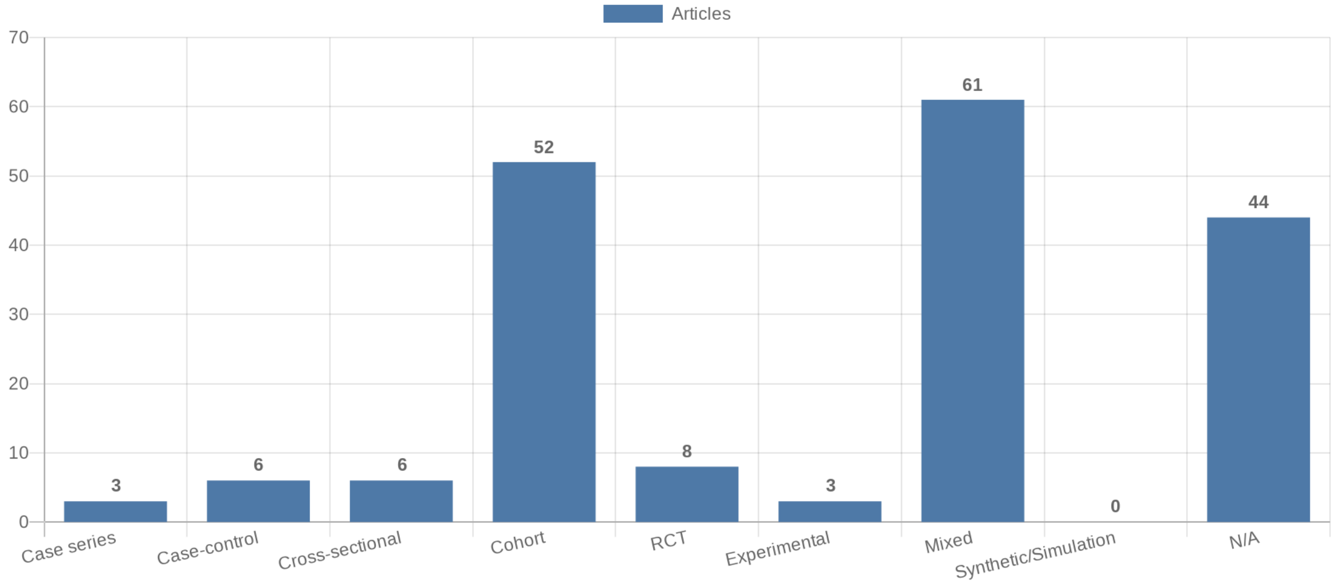

Figure 3. Study-type (directionality) distribution of included originals

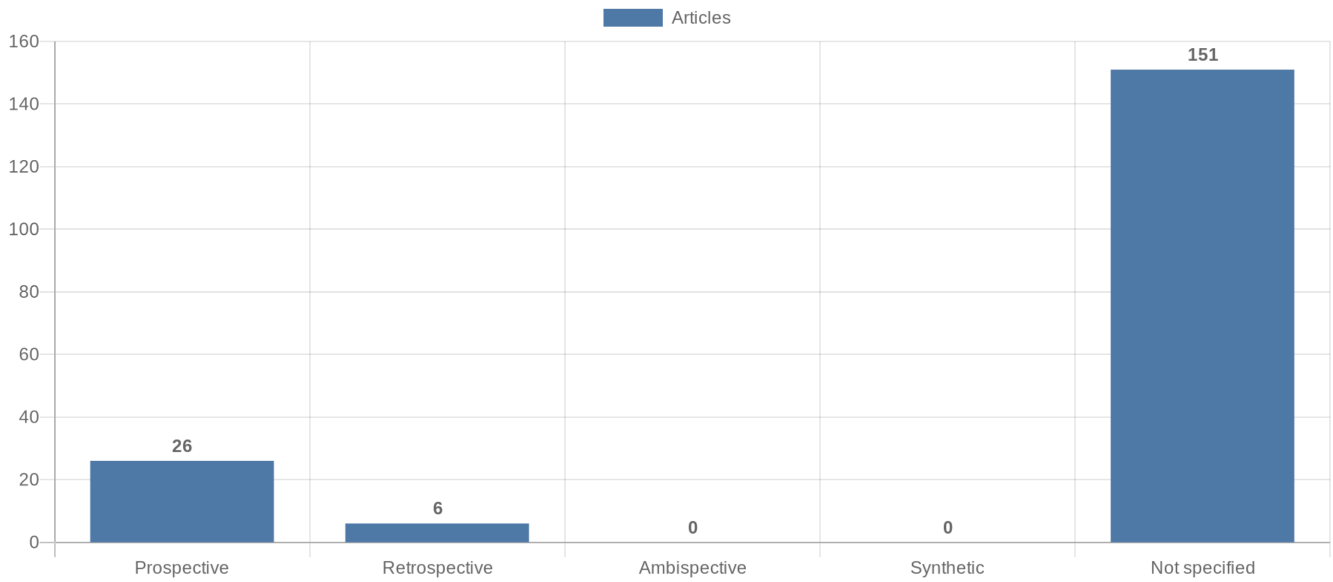

Figure 4. Main extracted research topics

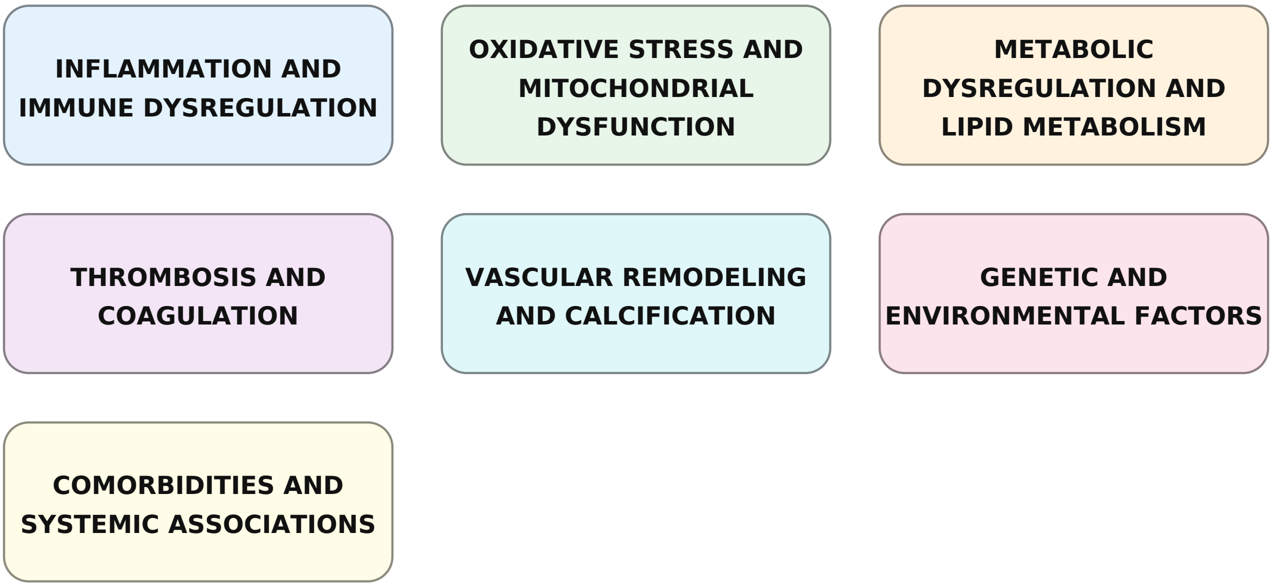

Figure 5. Limitations of current studies (topics)

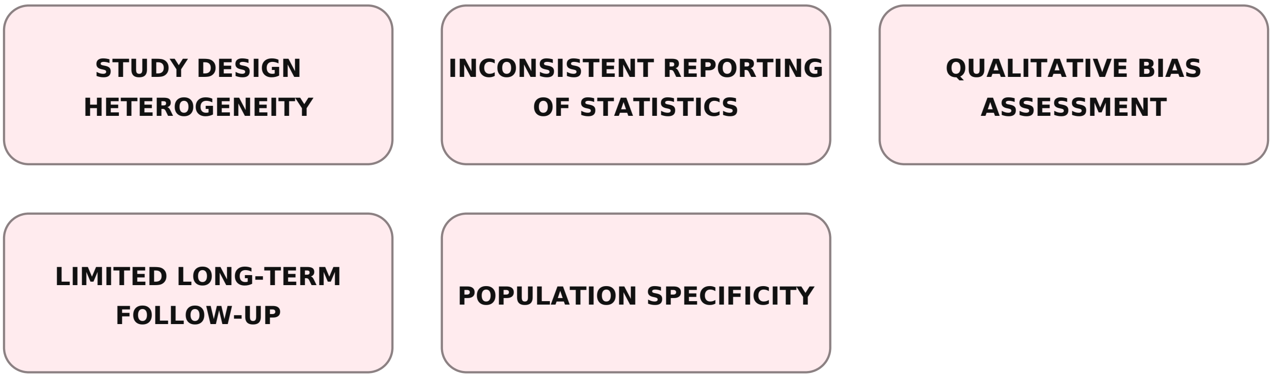

Figure 6. Future research directions (topics)