PAD Risk Factors: Systematic Review with ☸SAIMSARA

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Abstract: The aim of this paper is to identify and synthesize the key risk factors associated with peripheral artery disease based on a structured extraction summary of academic literature. The review utilises 261 studies with 2834010 total participants (naïve ΣN). The synthesis of current literature demonstrates that for men, each additional traditional cardiovascular risk factor (smoking, hypertension, hypercholesterolemia, and type 2 diabetes) was associated with a multivariable-adjusted hazard ratio of 2.06 (95% CI, 1.88–2.26) for PAD development over 25 years. This underscores the profound cumulative impact of these factors on PAD risk across diverse populations, particularly those with diabetes. The heterogeneity in study designs and populations represents a significant limitation, potentially affecting the generalizability of some findings. Therefore, a concrete next step involves designing large-scale, prospective cohort studies with standardized PAD diagnostic criteria to further elucidate the interplay of traditional and novel risk factors across diverse global populations, ultimately informing more precise preventive and therapeutic strategies.

Review Stats

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- Source: Semantic Scholar
- Scope: All fields
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
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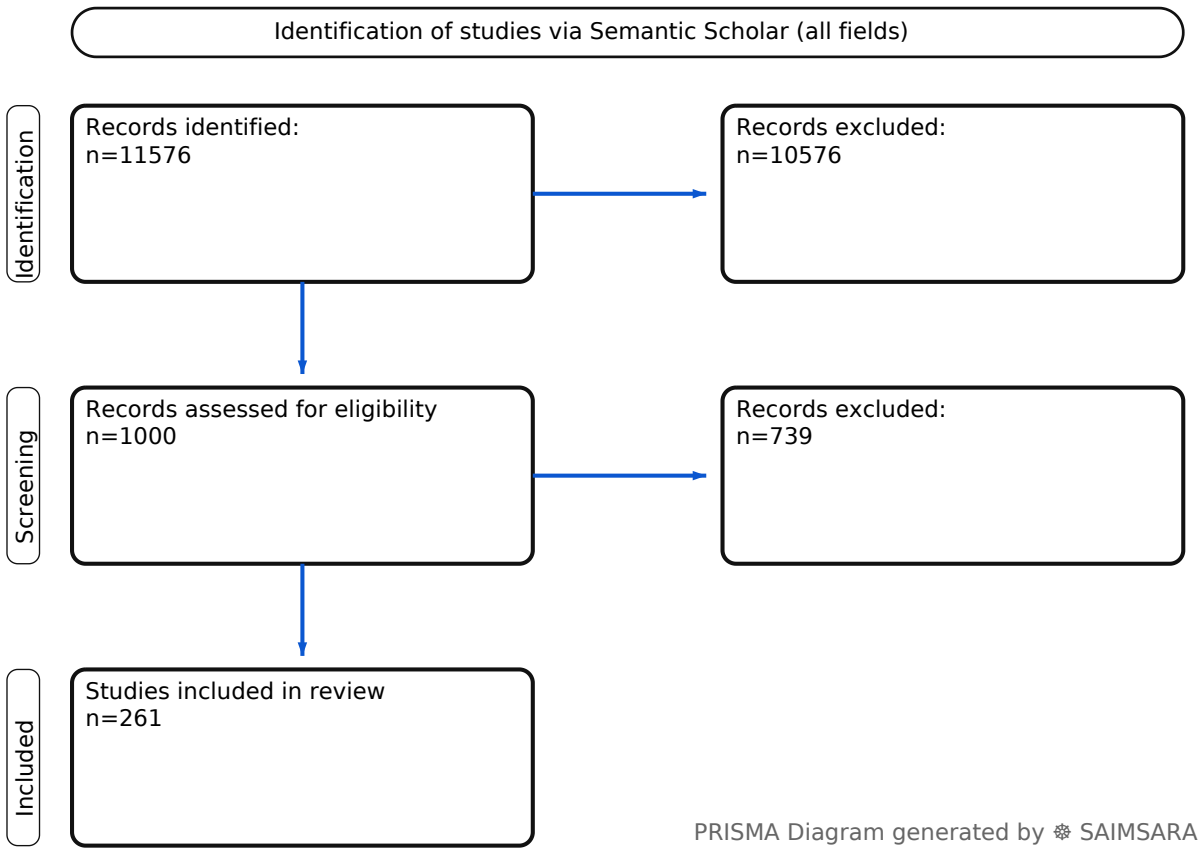
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 261
- Total study participants (naïve ΣN): 2834010


Identification of studies via Semantic Scholar (all fields)
Identification
Records identified:
n=11576
Records excluded:
n=10576
Screening
Records assessed for eligibility
n=1000
Records excluded:
n=739
Included
Studies included in review
n=261
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
pad risk factors → Outcome
0
Harmful for patients ΣN=266657 (94%)
Beneficial for patients ΣN=72427 (3%)
Neutral ΣN=94926 (3%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: Outcome Typical timepoints: 10-y, peri/post-op. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, mortality, healing.

Predictor: pad risk factors — exposure/predictor. Doses/units seen: 60 g, 25 kg, 17 ml, 100 g, 60 ml, 45 ml. Routes seen: iv, oral. Typical comparator: individuals with only pad, control, those with coronary artery, coronary….

- **1) Beneficial for patients** — Outcome with pad risk factors — [18], [72], [76], [82], [97], [192], [214], [255] — ΣN=72427
- **2) Harmful for patients** — Outcome with pad risk factors — [1], [2], [4], [5], [6], [7], [8], [10], [11], [12], [13], [14], [15], [16], [17], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [52], [53], [54], [55], [66], [68], [69], [70], [71], [73], [74], [75], [77], [78], [79], [80], [81], [84], [85], [88], [89], [90], [91], [92], [93], [94], [95], [98], [99], [100], [101], [104], [105], [107], [109], [110], [112], [113], [114], [115], [117], [119], [120], [121], [122], [124], [125], [127], [129], [131], [133], [134], [135], [136], [137], [138], [139], [140], [141], [143], [147], [148], [149], [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], [178], [179], [180], [181], [182], [183], [184], [185], [187], [188], [189], [190], [191], [193], [194], [196], [197], [198], [199], [200], [201], [202], [203], [204], [205], [206], [207], [210], [213], [216], [218], [219], [220], [222], [223], [224], [225], [226], [227], [228], [229], [233], [234], [235], [236], [238], [239], [241], [242], [243], [244], [245], [246], [247], [248], [249], [252], [253], [254], [257], [258], [259], [260] — ΣN=2666657
- **3) No clear effect** — Outcome with pad risk factors — [3], [9], [51], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [67], [83], [86], [87], [96], [102], [103], [106], [108], [111], [116], [118], [123], [126], [128], [130], [132], [142], [144], [145], [146], [177], [186], [195], [208], [209], [211], [212], [215], [217], [221], [230], [231], [232], [237], [240], [250], [251], [256], [261] — ΣN=94926

1) Introduction

Peripheral artery disease (PAD) is a prevalent atherosclerotic condition affecting the arteries supplying blood to the limbs, most commonly the legs. It is a significant public health concern

associated with substantial morbidity and mortality, including increased risks of cardiovascular events, stroke, and limb-related complications such as amputation [1, 104, 170, 244]. Understanding the multifaceted risk factors contributing to PAD development and progression is crucial for effective prevention, early diagnosis, and targeted management strategies. This paper systematically synthesizes current evidence on PAD risk factors, drawing exclusively from a structured extraction summary to provide a comprehensive overview.

2) Aim

The aim of this paper is to identify and synthesize the key risk factors associated with peripheral artery disease 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. Cohort studies and randomized controlled trials (RCTs) generally offer stronger evidence for associations and causality than cross-sectional or mixed designs. The summary includes a variety of study designs, suggesting a potential for varied levels of evidence strength across findings. Many studies did not specify directionality, which can limit causal inference.

4) Results

4.1 Study characteristics

The included studies predominantly comprised cohort, cross-sectional, and mixed designs, with a few randomized controlled trials. Populations varied widely, including individuals with type 2 diabetes (T2D) [1, 2, 13, 18], HIV-infected patients [15, 40], general community-dwelling adults [14, 98], and specific patient cohorts such as those with chronic kidney disease or undergoing hemodialysis [65, 143]. Follow-up periods, when specified, ranged from 90 days to 39 years [8, 97].

4.2 Main numerical result aligned to the query

The cumulative impact of traditional cardiovascular risk factors significantly increases the likelihood of developing peripheral artery disease. For men, each additional risk factor (smoking, hypertension, hypercholesterolemia, and type 2 diabetes) was associated with a multivariable-adjusted hazard ratio (HR) of 2.06 (95% CI, 1.88–2.26) for PAD development over 25 years [37]. Similarly, individuals with type 2 diabetes who had all five PAD risk factors not at target showed a substantially higher adjusted hazard ratio for PAD of 9.28 (95% CI 3.62-23.79) compared to 1.41 (95% CI 1.23-1.63) for those with all risk factors within target [2].

4.3 Topic synthesis

- **Diabetes Mellitus and Glycemic Control:** Type 2 diabetes (T2D) is a consistently identified major risk factor for PAD, with a median odds ratio (OR) of approximately 2.66 [55] (range 1.42–5.8 [16, 34, 138, 253]) and is associated with increased mortality [1] and faster ankle-brachial index (ABI) decline [46]. High HbA1c levels [10, 13, 26, 44, 148, 185, 205] and longer diabetes duration [10, 13, 258] are also significant contributors. Metabolic syndrome (MetS) in both type 1 and type 2 diabetes significantly increases PAD risk [6, 136].
- **Smoking and Tobacco Use:** Smoking is a primary and highly influential risk factor for PAD, with a median OR of 3.0 [20, 34, 42, 55] (range 1.37–7.2 [16, 20, 34, 42, 55]) and accounts for a substantial proportion of PAD risk (45.6% [43]). It is more strongly associated with PAD risk in women than men [7] and is linked to increased major adverse limb events (MALE) [24]. Genetic liability to smoking is also associated with increased PAD risk [171].
- **Hypertension and Blood Pressure Regulation:** High systolic blood pressure (SBP) and hypertension are consistently linked to PAD, with a median OR of 1.7 [42] (range 1.44–3.8 [16, 20, 30, 34, 42]) and are primary attributable risk factors, particularly for females [5]. Pulse pressure [14, 44] and 24-hour SBP [13] are also associated with PAD development/progression.
- **Dyslipidemia and Lipoprotein Metabolism:** Elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and dyslipidemia are significant risk factors [3, 13, 25, 34, 35, 49, 50, 53, 113, 119, 198, 200]. Apolipoprotein B (ApoB) and remnant cholesterol are identified as major causal lipoprotein-related factors for PAD [12, 173]. Low high-density lipoprotein cholesterol (HDL-C) is also associated with PAD, particularly in women [7, 99, 113, 152].
- **Inflammatory and Novel Biomarkers:** Elevated high-sensitivity C-reactive protein (hs-CRP) is a significant risk factor [20, 34, 41, 103, 114, 124, 131, 164, 176, 212]. Other emerging biomarkers include high plasma homocysteine (Hcy) [19, 34, 41, 51], triglyceride-glucose (TyG) index [66, 70], copeptin, N-BNP, cystatin C [68, 69], urinary fatty acid binding protein 3 (uFABP3) [100], sortilin [218, 225], asprosin [224], and specific immune-inflammation indices (NHR, MHR, PHR, SII, SIRI, AISI) [202].
- **Genetic and Socioeconomic Factors:** Genetic liability for major depressive disorder (MDD) is associated with increased PAD risk [4]. Specific genetic loci (IPO5/RAP2A, EDNRA, HDAC9, ATXN2-SH2B3, SLC2A10) and selenoprotein gene polymorphisms are linked to PAD susceptibility [129, 201, 233, 257]. Low individual- and area-level socioeconomic status (SES) are strong predictors of PAD hospitalization [75, 105, 111, 182], and race/ethnicity also plays a role in lifetime risk [73, 152].
- **Comorbid Conditions and Lifestyle:** Advanced age is a consistent risk factor [1, 10, 13, 14, 20, 26, 30, 31, 35, 36, 44, 48, 53, 55, 68, 78, 97, 103, 104, 107, 115, 130, 133, 152, 156,

157, 159, 161, 163, 166, 167, 169, 200, 204, 238, 247, 248, 254, 258]. Obesity (BMI ≥ 25 kg/m²) [21, 27, 50, 113, 114, 119, 122, 153, 159, 165, 186, 216] and chronic kidney disease (CKD) [10, 22, 28, 49, 65, 83, 105, 137, 143, 145, 160, 163, 166, 210, 254] are significant. Other factors include HIV infection [15, 40, 142, 164], atrial fibrillation (AF) [54, 81, 93, 104], major depressive disorder (MDD) [4, 71, 243], metabolic syndrome [6, 27, 29, 49, 136], and a sedentary lifestyle [36]. A favorable lifestyle is associated with lower PAD risk [18], while insomnia [11] and job strain [187] are identified as risk factors.

5) Discussion

5.1 Principal finding

The synthesis reveals that for men, each additional traditional cardiovascular risk factor (smoking, hypertension, hypercholesterolemia, and type 2 diabetes) increases the hazard of PAD development by 2.06-fold (95% CI, 1.88–2.26) [37]. This highlights the compounding effect of multiple risk factors on PAD incidence.

5.2 Clinical implications

- **Early Screening in High-Risk Individuals:** Patients with multiple traditional cardiovascular risk factors, particularly those with type 2 diabetes, should undergo early and regular screening for PAD, even in the absence of overt symptoms, given the substantial increase in risk with compounding factors [2, 37].
- **Intensified Risk Factor Management:** Comprehensive management targeting smoking cessation, blood pressure control, dyslipidemia, and glycemic control is critical for patients at risk of or with established PAD, as suboptimal treatment is prevalent and directly impacts outcomes [3, 106].
- **Sex-Specific Risk Assessment:** Clinicians should consider sex-specific differences in PAD risk factor associations, such as smoking and stroke history having a greater impact on PAD risk in women, and higher HDL-C being more protective in women [7, 16].
- **Monitoring Beyond Traditional Factors:** Beyond traditional risk factors, monitoring for conditions like chronic kidney disease, HIV infection, and inflammatory biomarkers (e.g., hs-CRP, homocysteine) should be integrated into PAD risk assessment, especially in vulnerable populations [19, 40, 124, 143].
- **Lifestyle Interventions:** Promoting favorable lifestyle interventions, including physical activity and healthy diet, is crucial, as they are associated with a lower risk of PAD, independent of genetic predisposition [18, 76, 192].

5.3 Research implications / key gaps

- **Standardized Diagnostic Criteria:** Research is needed to develop and validate standardized diagnostic criteria for asymptomatic PAD across diverse populations to ensure consistent early detection and intervention [116].
- **Longitudinal Biomarker Studies:** Prospective longitudinal studies are required to further elucidate the causal pathways and prognostic value of novel inflammatory and metabolic biomarkers (e.g., sortilin, asprosin, TyG index) in PAD development and progression [66, 70, 218, 224].
- **Interventional Trials for Lifestyle:** Randomized controlled trials are needed to assess the effectiveness of targeted lifestyle interventions (e.g., specific dietary patterns, exercise regimens) in reducing PAD incidence and improving outcomes across different risk factor profiles [18, 76, 192].
- **Genetic-Environmental Interactions:** Future research should explore complex genetic-environmental interactions and their influence on PAD susceptibility, moving beyond single gene associations to polygenic risk scores and their interplay with modifiable risk factors [129, 201, 239, 257].
- **Socioeconomic Disparities:** Studies are needed to understand the mechanisms by which socioeconomic status and race/ethnicity independently affect PAD risk and outcomes, informing targeted public health interventions to reduce disparities [73, 75, 105, 111, 182].

5.4 Limitations

- **Heterogeneous Study Designs** — The review includes a variety of study designs, from cross-sectional to cohort studies, which limits the ability to draw definitive causal conclusions due to varying levels of evidence.
- **Variability in PAD Definitions** — Different studies may use varied criteria for PAD diagnosis (e.g., ABI thresholds, symptomatic vs. asymptomatic), potentially affecting the comparability and generalizability of prevalence and risk estimates.
- **Incomplete Data on Interventions** — While risk factors are identified, the summary provides limited information on the effectiveness of specific interventions or treatment thresholds for mitigating these risks, creating a gap in translational knowledge.
- **Geographic and Population Bias** — Many studies are focused on specific geographic regions (e.g., China, Japan, Saudi Arabia) or populations (e.g., T2D patients, HIV-infected), which may limit the generalizability of findings to broader global populations.
- **Underreporting of PAD** — Adults with lower-limb loss may underreport PAD, suggesting that the true prevalence and impact of risk factors could be higher than observed in some studies [9].

5.5 Future directions

- **Standardized PAD Diagnosis** — Implement consistent diagnostic criteria for PAD across research and clinical settings.
- **Longitudinal Biomarker Validation** — Conduct large-scale prospective studies to validate novel PAD biomarkers.
- **Targeted Lifestyle Interventions** — Design and test personalized lifestyle interventions for PAD prevention.
- **Genetic Risk Stratification** — Develop and integrate genetic risk scores into PAD prediction models.
- **Health Equity Research** — Investigate and address socioeconomic and racial disparities in PAD.

6) Conclusion

The synthesis of current literature demonstrates that for men, each additional traditional cardiovascular risk factor (smoking, hypertension, hypercholesterolemia, and type 2 diabetes) was associated with a multivariable-adjusted hazard ratio of 2.06 (95% CI, 1.88–2.26) for PAD development over 25 years [37]. This underscores the profound cumulative impact of these factors on PAD risk across diverse populations, particularly those with diabetes. The heterogeneity in study designs and populations represents a significant limitation, potentially affecting the generalizability of some findings. Therefore, a concrete next step involves designing large-scale, prospective cohort studies with standardized PAD diagnostic criteria to further elucidate the interplay of traditional and novel risk factors across diverse global populations, ultimately informing more precise preventive and therapeutic strategies.

References

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Figure 1. Publication-year distribution of included originals

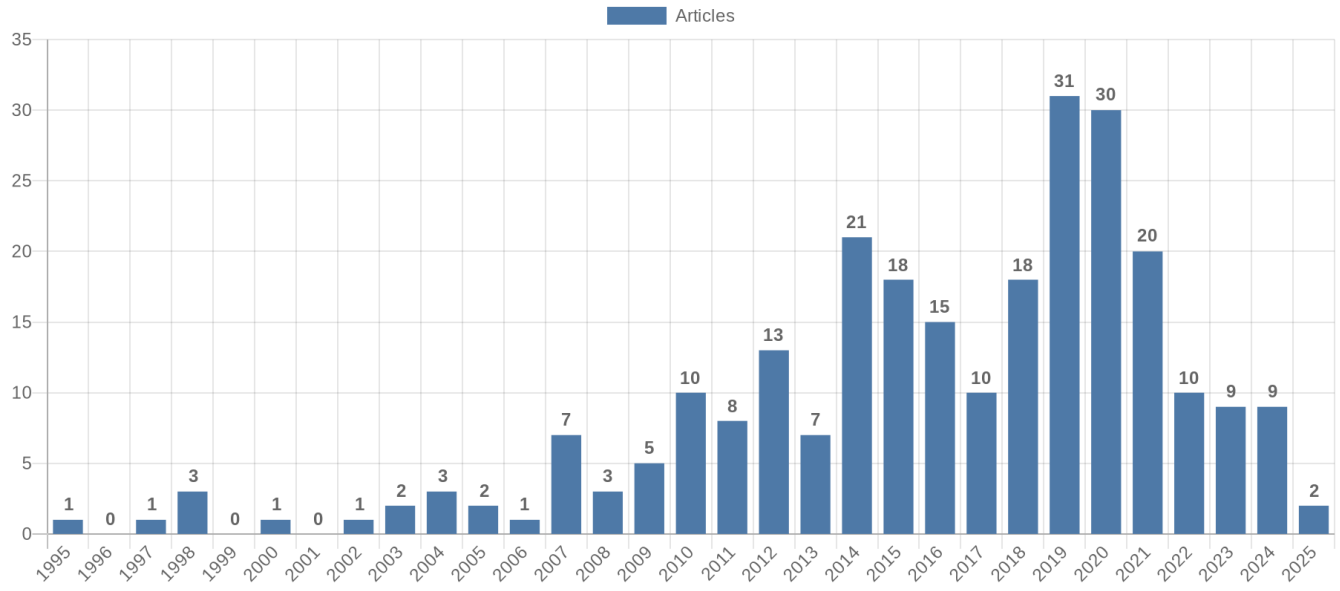

Figure 2. Study-design distribution of included originals

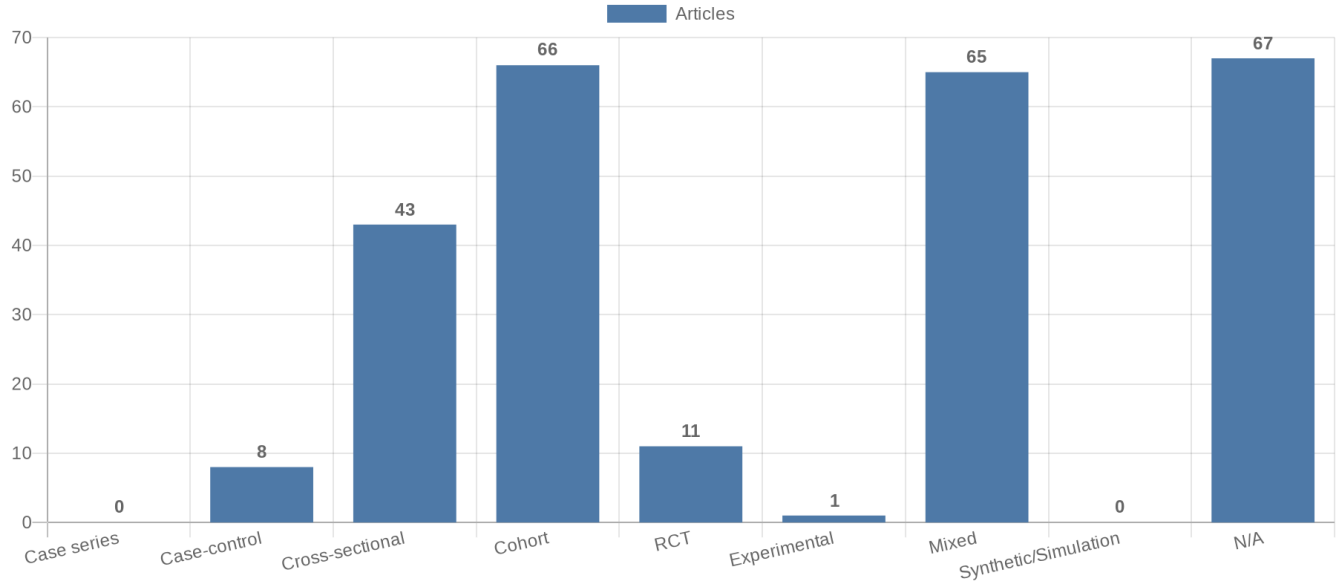

Figure 3. Study-type (directionality) distribution of included originals

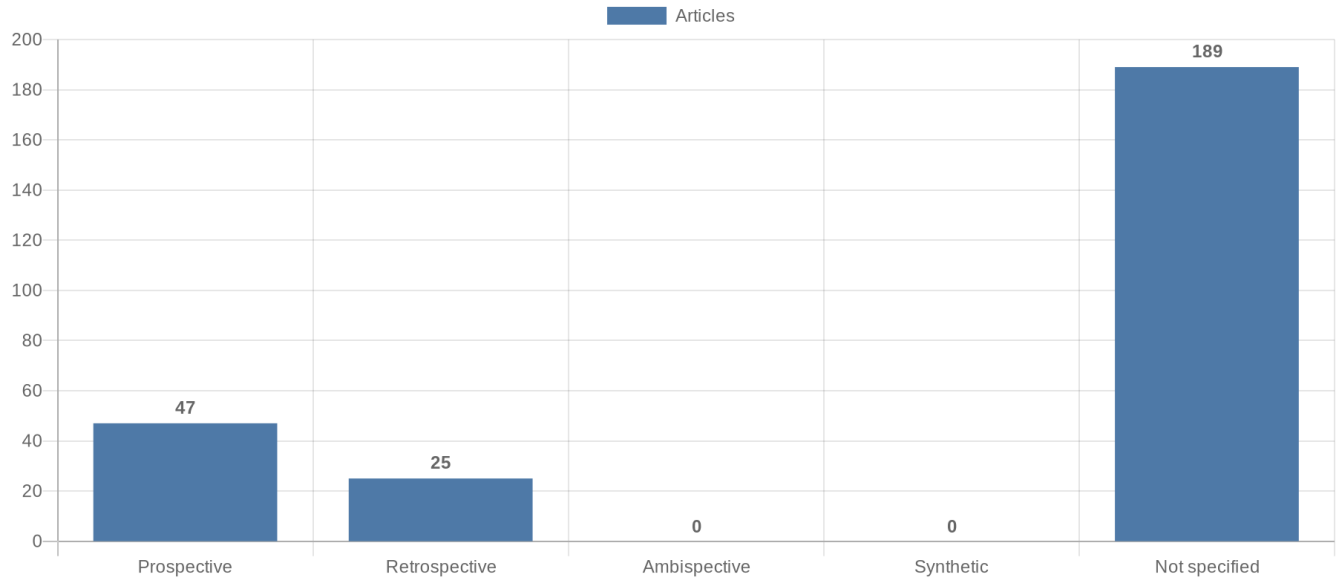

Figure 4. Main extracted research topics

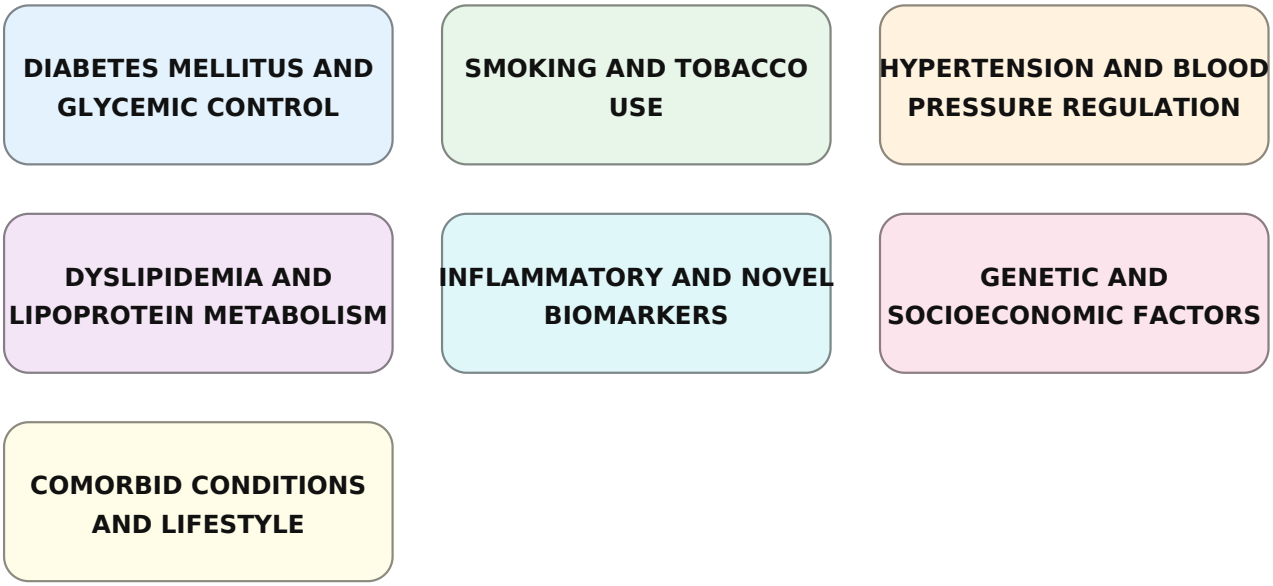

Figure 5. Limitations of current studies (topics)

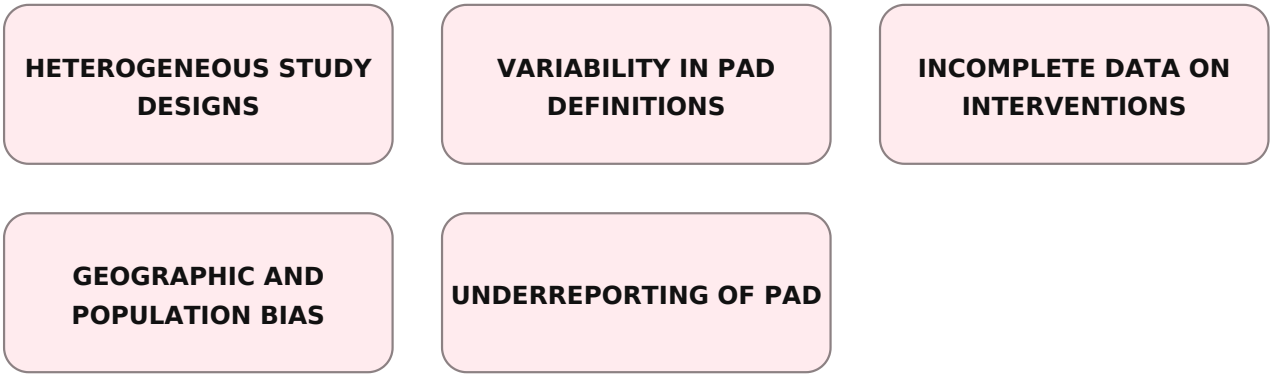

Figure 6. Future research directions (topics)