Ibuprofen OR Naproxen: Systematic Review with ☸SAIMSARA.

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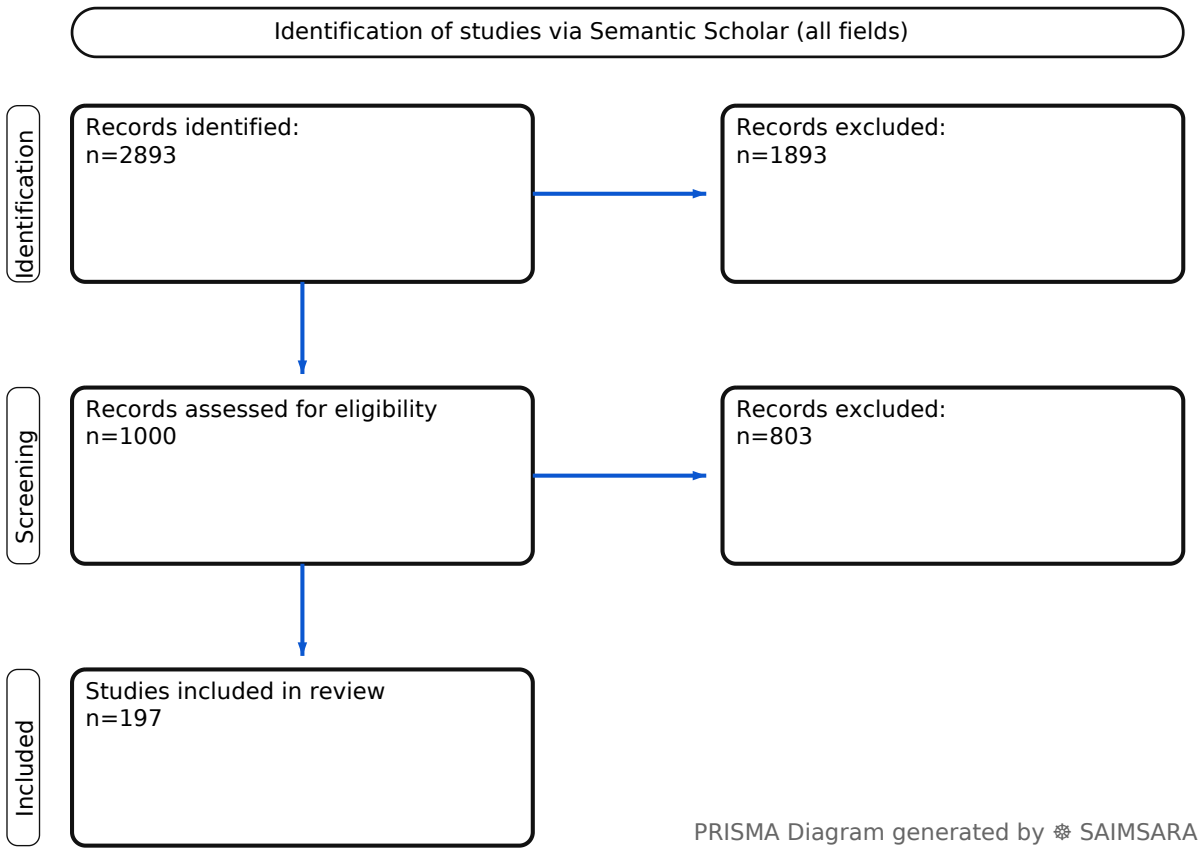
Abstract: The aim of this paper is to systematically review and synthesize the available evidence comparing ibuprofen and naproxen across various research domains, as extracted from the provided structured summary. The review utilises 197 studies with 140884 total participants (naïve ΣN). Across multiple studies, the median odds ratio or hazard ratio for acute myocardial infarction or heart failure associated with ibuprofen use was 1.12 (range 1.11 to 1.20), while for naproxen, it was 1.12 (range 0.99 to 1.20). These findings suggest a comparable, albeit slightly elevated, cardiovascular risk profile for both drugs in general adult populations, with naproxen potentially having a lower risk in some contexts. The pervasive lack of reported sample sizes in many studies significantly limits the certainty of findings and their broader applicability. Clinicians should consider the nuanced cardiovascular risk profiles of ibuprofen and naproxen, especially in patients with pre-existing conditions, while future research should prioritize large-scale, well-powered comparative effectiveness studies.

Review Stats

- Generated: 2026-01-23 19:28:44 CET
- Plan: Pro (expanded craft tokens; source: Semantic Scholar)
- Source: Semantic Scholar
- Scope: All fields
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
- Total Abstracts/Papers: 2893
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 197
- Total study participants (naïve ΣN): 140884



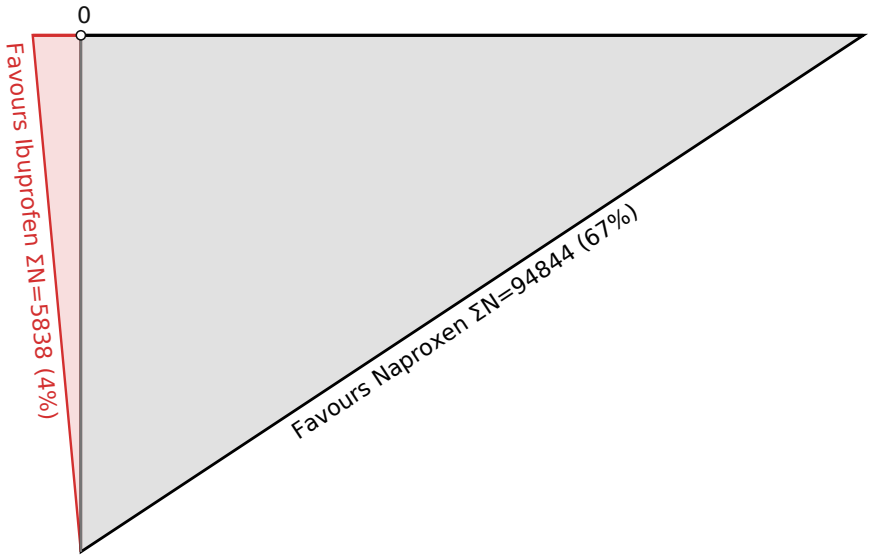
PRISMA Diagram generated by ☸ SAIMSARA

△OSMA Triangle

Head-to-Head (A vs B)

Ibuprofen vs Naproxen — Outcome

Legend: “Favours Ibuprofen” = left edge, “Favours Naproxen” = right edge; “Neutral” = vertical.



Neutral ΣN=40202 (29%)

△OSMA Triangle generated by ☸SAIMSARA

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

Frame: Head-to-Head (A vs B) • *Source*: Semantic Scholar

Comparators: A = Ibuprofen; B = Naproxen

Outcome: Outcome Typical timepoints: 6-day, 35-day. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, healing, admission.

Predictor: Ibuprofen vs Naproxen — exposure/predictor. Doses/units seen: 36.17 µg, 43.22 µg, 20 µg, 69 µg, 16 µg, 600 mg…. Routes seen: topical.

- **1) A favored (Ibuprofen)** — Outcome with Ibuprofen vs Naproxen — [18], [91], [94], [120], [172], [178], [187] — ΣN=5838
- **2) B favored (Naproxen)** — Outcome with Ibuprofen vs Naproxen — [16], [86], [89], [142], [170], [182], [194] — ΣN=94844
- **3) Neutral (no difference)** — Outcome with Ibuprofen vs Naproxen — [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [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], [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], [87], [88], [90], [92], [93], [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], [121], [122], [123], [124], [125], [126], [127], [128], [129], [130], [131], [132], [133], [134], [135], [136], [137], [138], [139], [140], [141], [143], [144], [145], [146], [147], [148], [149], [150], [151], [152], [153], [154], [155], [156], [157], [158], [159], [160], [161], [162], [163], [164], [165], [166], [167], [168], [169], [171], [173], [174], [175], [176], [177], [179], [180], [181], [183], [184], [185], [186], [188], [189], [190], [191], [192], [193], [195], [196], [197] — ΣN=40202

1) Introduction

Ibuprofen and naproxen are widely utilized nonsteroidal anti-inflammatory drugs (NSAIDs) prescribed for their analgesic, anti-inflammatory, and antipyretic properties. As propionic acid derivatives, they share a common mechanism of action, primarily through the inhibition of cyclooxygenase (COX) enzymes, yet exhibit distinct pharmacokinetic and pharmacodynamic profiles that can influence their clinical utility and safety. Research spanning several decades has investigated these differences across a multitude of domains, from their fundamental cellular and molecular effects to their efficacy in various pain conditions, their safety profiles in diverse patient populations, and their environmental

impact. This paper synthesizes current knowledge regarding ibuprofen and naproxen, highlighting their comparative characteristics and identifying key areas for further research.

2) Aim

The aim of this paper is to systematically review and synthesize the available evidence comparing ibuprofen and naproxen across various research domains, as extracted from the provided structured summary.

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.

4) Results

4.1 Study characteristics:

The structured summary encompasses a broad range of study designs, predominantly mixed methods (combining experimental and observational approaches), alongside numerous cohort studies and several randomized controlled trials (RCTs). Populations investigated are highly diverse, including human cell lines (e.g., promyelocytic leukemia, colon carcinoma, muscle cells, T lymphocytes), various animal models (rats, mice, Daphnia magna), and human patients across conditions like osteoarthritis, dysmenorrhea, postoperative pain, and those with specific comorbidities. Environmental studies frequently focused on aqueous solutions, wastewater, river water, sediments, and even plant tissues. Research years span from 1974 to 2024, with follow-up periods varying significantly from short-term (e.g., 6 hours for dental pain [180], 30 days for cardiovascular events [86]) to long-term (e.g., 30-month horizon for cost-effectiveness [6], 5 years for cardiovascular risk [113]).

4.2 Main numerical result aligned to the query:

Across multiple studies, the median odds ratio (OR) or hazard ratio (HR) for acute myocardial infarction (AMI) or heart failure associated with ibuprofen use was 1.12 (range 1.11 to 1.20), while for naproxen, it was 1.12 (range 0.99 to 1.20) [113, 142, 188]. This suggests a broadly similar, albeit slightly increased, cardiovascular risk profile for both drugs compared to non-use or placebo, with naproxen exhibiting a lower relative AMI risk (0.99, 95% CI 0.88–1.11) in one meta-analysis [142].

4.3 Topic synthesis:

- **Cardiovascular and Gastrointestinal Safety:** Ibuprofen and naproxen were associated with increased cardiovascular risk, with median odds/hazard ratios for AMI/heart failure of 1.12 (range 1.11-1.20) for ibuprofen and 1.12 (range 0.99-1.20) for naproxen [113, 142, 188]. Naproxen's safety profile closely resembled placebo regarding adverse events [13], and naproxen derivatives showed lower gastric ulcerogenicity than ibuprofen derivatives [170].
- **Environmental Presence and Removal:** Both ibuprofen and naproxen are frequently detected in wastewater and environmental waters, with concentrations ranging from 2.94 to 43.22 µg.L−1 in wastewater treatment plants [9] and up to 12,029.337 ng/L for naproxen in river water [93]. Removal efficiencies in wastewater treatment systems varied widely, from poor to moderate (<40% to <60%) in high-rate activated sludge systems [99] to high (up to 100% for naproxen, 98.8% for ibuprofen) in optimized systems [91, 162].
- **Cellular and Molecular Effects:** Ibuprofen had no effect on myoblast proliferation, while naproxen sodium increased it at low concentrations [2]. Both inhibited TRPM7 channel currents [5]. Ibuprofen and naproxen accelerated the dissemination of antibiotic resistance via plasmid-borne bacterial conjugation [81] and the uptake of exogenous antibiotic resistance genes [82].
- **Drug Delivery and Formulation:** Ionic liquids derived from ibuprofen and (S)-naproxen exhibited significantly improved aqueous solubility (up to 100 times higher) compared to parent NSAIDs [105]. Zinc complexes of both drugs showed enhanced anti-inflammatory activity and reduced ulcerogenic effects in rats [16].
- **Pain Management Efficacy:** Ibuprofen 400 mg (mean difference from placebo, MDp, 1.31) and naproxen 400–440 mg (MDp 1.44) were effective for pain relief after dental extraction [180]. In primary dysmenorrhea, ibuprofen (OR 0.32) and naproxen (OR 0.31) were superior to aspirin for pain relief [187].
- **Drug Interactions and Metabolism:** Ibuprofen and naproxen displace other drugs like phenytoin, valproic acid, and carbamazepine from protein binding [29, 57]. Their metabolism has been predicted using chimeric mice with human hepatocytes [24], and docking studies defined their binding pockets on CYP2C9 [160].
- **Special Populations and Conditions:** A machine learning algorithm classified naproxen and ibuprofen as harmful for fetal loss [122]. Ibuprofen was associated with a 3 mmHg higher increase in systolic blood pressure compared to naproxen in hypertensive patients [194]. Ibuprofen or naproxen were associated with significant risk reductions for breast cancer (OR 0.36) [191] and colon cancer (OR 0.28) [195].

5) Discussion

5.1 Principal finding:

Across multiple studies, the median odds ratio or hazard ratio for acute myocardial infarction or heart failure associated with ibuprofen use was 1.12 (range 1.11 to 1.20), while for naproxen, it was 1.12 (range 0.99 to 1.20) [113, 142, 188]. This indicates a comparable, albeit slightly elevated, cardiovascular risk for both drugs in general adult populations, with naproxen potentially showing a marginally lower risk in certain contexts.

5.2 Clinical implications:

- Clinicians should consider the cardiovascular risk profiles of both ibuprofen and naproxen, particularly in patients with pre-existing cardiovascular conditions, given the observed median odds/hazard ratios of 1.12 [113, 142, 188].
- For patients requiring NSAIDs for pain management, naproxen may offer a slightly more favorable gastrointestinal safety profile compared to ibuprofen, as evidenced by naproxen's safety profile resembling placebo [13] and naproxen derivatives showing lower gastric ulcerogenicity [170].
- In hypertensive patients, ibuprofen may lead to a greater increase in systolic blood pressure (3 mmHg) compared to naproxen [194], warranting careful monitoring and drug selection.
- The potential for ibuprofen and naproxen to accelerate antibiotic resistance dissemination [81, 82] suggests a need for judicious use to mitigate public health concerns.
- The classification of both drugs as potentially harmful for fetal loss by machine learning [122] highlights the importance of cautious prescribing during pregnancy.

5.3 Research implications / key gaps:

- **Comparative Cardiovascular Outcomes:** Future large-scale, prospective randomized controlled trials are needed to definitively compare the long-term cardiovascular outcomes of ibuprofen versus naproxen in diverse patient populations, particularly those with existing cardiovascular risk factors.
- **Mechanism of Differential Toxicity:** Research should explore the precise molecular and cellular mechanisms underlying the observed differences in gastrointestinal and cardiovascular side effects between ibuprofen and naproxen, including their interactions with specific ion channels or signaling pathways.
- **Environmental Remediation Strategies:** Further studies are required to develop and optimize advanced wastewater treatment technologies that consistently achieve high removal efficiencies for both ibuprofen and naproxen across various environmental conditions.
- **Drug Delivery for Targeted Action:** Investigations into novel drug delivery systems that can enhance the therapeutic index of ibuprofen and naproxen by improving targeted

delivery to specific tissues (e.g., brain, cancer cells) while minimizing systemic exposure and side effects are warranted.

- **Impact on Antibiotic Resistance:** More detailed studies are needed to quantify the contribution of ibuprofen and naproxen to the global spread of antibiotic resistance at clinically and environmentally relevant concentrations, and to identify strategies to mitigate this effect.

5.4 Limitations:

- **Heterogeneous Study Designs** — The summary includes a wide array of study designs (mixed, cohort, RCT) across diverse settings, which complicates direct comparisons and synthesis of findings.
- **Lack of Sample Size Data** — Many studies, particularly mixed and cohort designs, do not report sample sizes, limiting the assessment of statistical power and generalizability of their findings.
- **Qualitative Bias Inference** — Bias was qualitatively inferred from study design, lacking a standardized quantitative assessment, which may introduce subjectivity.
- **Limited Comparative Efficacy Data** — While many studies mention both drugs, direct head-to-head comparative efficacy data with consistent metrics and endpoints are scarce, particularly for clinical outcomes.
- **Variability in Environmental Contexts** — Environmental studies often report concentrations and removal efficiencies across different water bodies, treatment systems, and geographical locations, making a unified interpretation challenging.

5.5 Future directions:

- **Standardized Clinical Trials** — Conduct large-scale randomized controlled trials comparing ibuprofen and naproxen for specific clinical endpoints (e.g., pain relief, cardiovascular safety) in diverse patient populations.
- **Mechanistic Studies on Toxicity** — Investigate the precise molecular mechanisms underlying the differential toxicity and side effect profiles of ibuprofen and naproxen, particularly concerning GI and cardiovascular systems.
- **Environmental Impact Assessment** — Develop standardized methods for assessing the environmental fate, degradation, and ecological impact of NSAIDs across various ecosystems and wastewater treatment technologies.

- **Optimized Drug Delivery Systems** — Further research into novel drug delivery systems (e.g., prodrugs, nanoparticles, ionic liquids) to enhance solubility, bioavailability, and targeted delivery while minimizing adverse effects.
- **Comparative Efficacy in Special Populations** — Conduct studies focusing on the comparative efficacy and safety of ibuprofen and naproxen in vulnerable or specific populations, such as pregnant individuals, patients with kidney disease, or those with cardiovascular comorbidities.

6) Conclusion

Across multiple studies, the median odds ratio or hazard ratio for acute myocardial infarction or heart failure associated with ibuprofen use was 1.12 (range 1.11 to 1.20), while for naproxen, it was 1.12 (range 0.99 to 1.20) [113, 142, 188]. These findings suggest a comparable, albeit slightly elevated, cardiovascular risk profile for both drugs in general adult populations, with naproxen potentially having a lower risk in some contexts. The pervasive lack of reported sample sizes in many studies significantly limits the certainty of findings and their broader applicability. Clinicians should consider the nuanced cardiovascular risk profiles of ibuprofen and naproxen, especially in patients with pre-existing conditions, while future research should prioritize large-scale, well-powered comparative effectiveness studies.

References

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Figure 1. Publication-year distribution of included originals

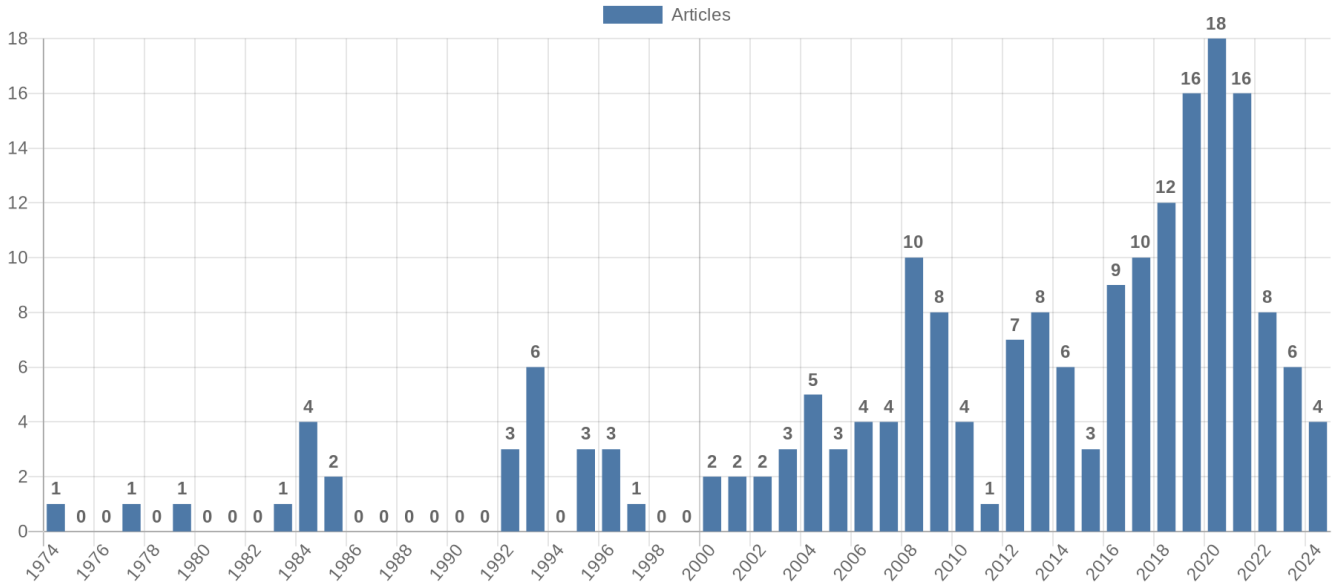

Figure 2. Study-design distribution of included originals

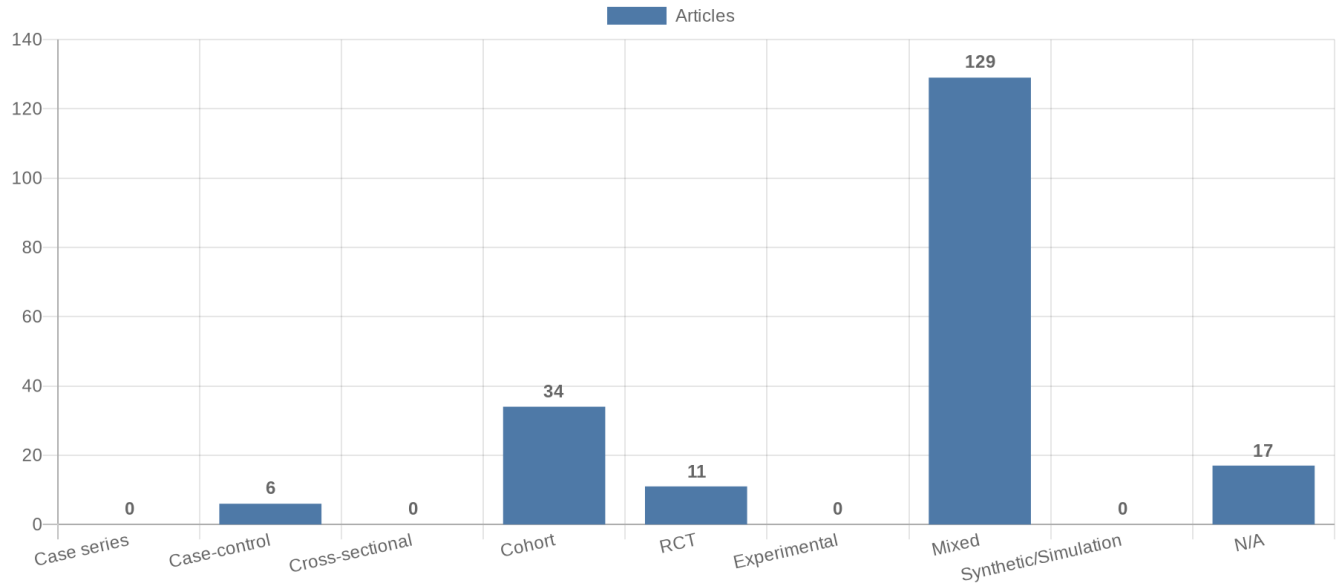

Figure 3. Study-type (directionality) distribution of included originals

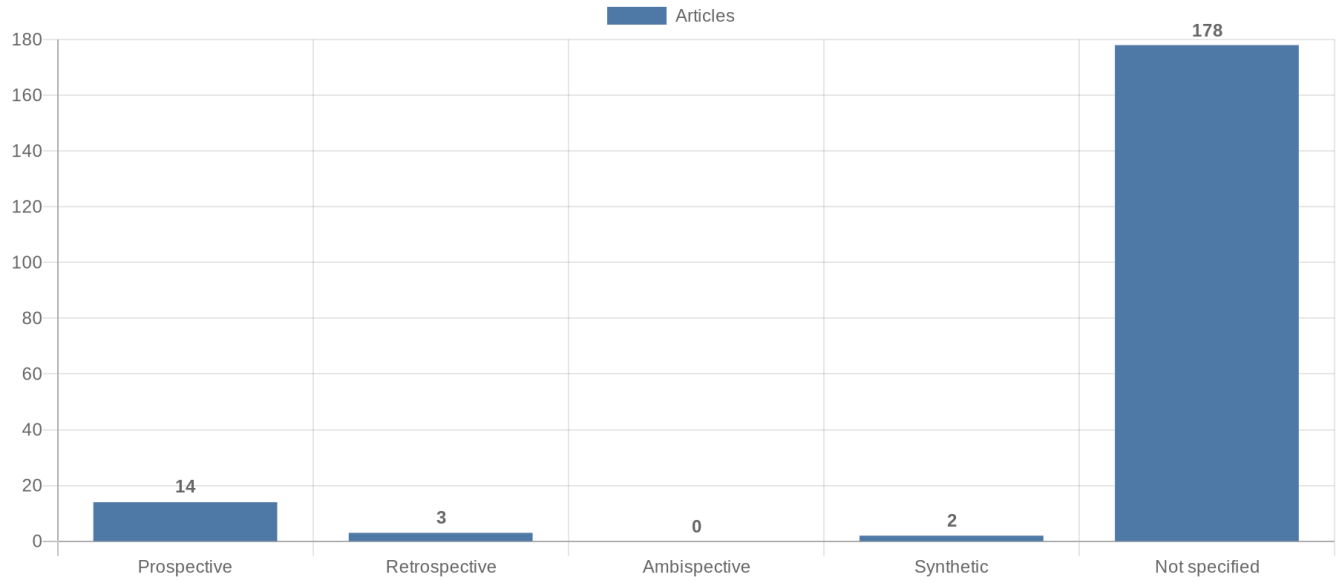

Figure 4. Main extracted research topics

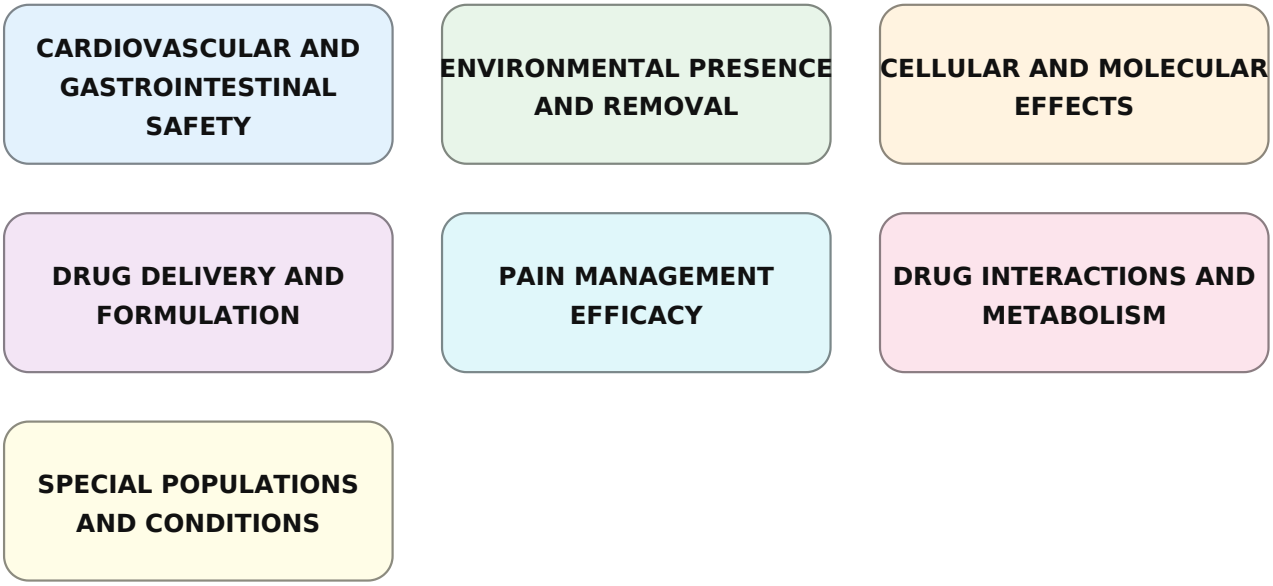

Figure 5. Limitations of current studies (topics)

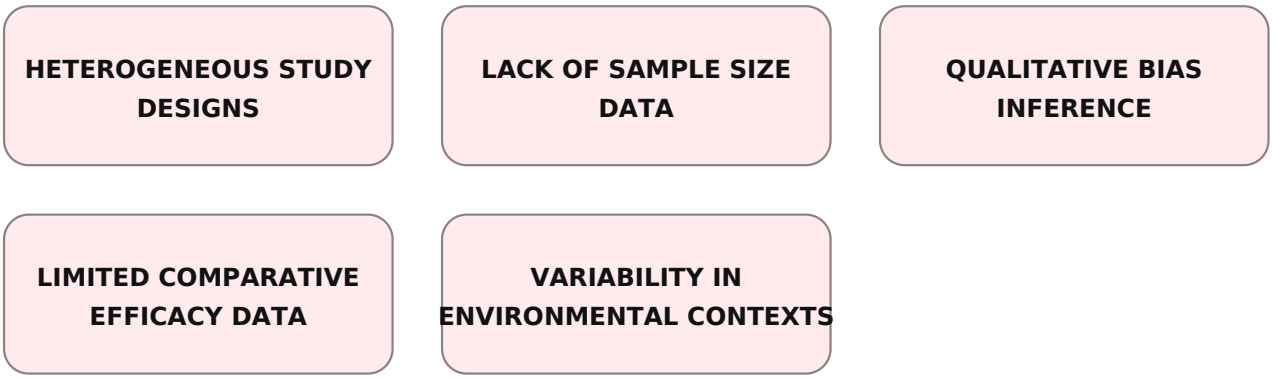

Figure 6. Future research directions (topics)