

Therapeutic Repositioning of SGLT2 Inhibitors Using Real-World Data: A Scoping Review of Emerging Indications and Rare Diseases

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Systematic Review

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Abstract

Background and Aims

Sodium-glucose cotransporter-2 inhibitors (SGLT2i), initially approved for type 2 diabetes mellitus, have progressively emerged as cardio-renal protective agents. Beyond glycaemic control, evidence indicates that SGLT2i act as systemic endocrine-metabolic modulators, via pleiotropic mechanisms including NLRP3 inflammasome inhibition, ketone-driven metabolic reprogramming, HIF-2 α -mediated erythropoietic effects, and uricosuric transporter activity. This scoping review maps Real-World Data (RWD)-based evidence on SGLT2i repositioning across these pathways and rare diseases.

Methods

A systematic search was conducted on PubMed and Scopus from inception to 31 May 2026, following PRISMA-ScR guidelines (OSF registration: 10.17605/OSF.IO/794CX). Eligibility followed a PCC framework (Population: any age/comorbidity; Concept: pleiotropic or off-label SGLT2i effects beyond approved cardio-renal indications; Context: real-world studies). Original peer-reviewed studies using RWD, including cohort studies and case series for rare diseases, were included. Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS) and the Murad et al. tool. Due to clinical and methodological heterogeneity, a narrative synthesis was performed.

Results

Seventy-four studies (2017–2026) were included, 66% published in 2024–2026. Research was concentrated in Asia (27 studies, NHIRD-based) and North America (24 studies, mainly EHR/TriNetX-based), with Europe contributing 16 studies. Seven thematic clusters were identified. Gout showed the most robust evidence (19 studies; median NOS 7; 30–50% risk reduction), driven by a uricosuric transporter-mediated mechanism. Anaemia (10 studies; +0.7–1.0 g/dL haemoglobin increase; up to 64% reduction in erythropoiesis-stimulating agents) showed signals consistent with genuine erythropoietic stimulation rather than haemoconcentration. Rare metabolic-transport diseases (13 studies; median Murad score 7), including glycogen storage disease type 1b and Fanconi-Bickel syndrome, represented a context where RWD provided the only available evidence, including off-label empagliflozin use in 21 infants with GSD type 1b. COPD (9 studies; 19–38% exacerbation reduction), neuroprotection, hepatoprotection and oncology showed promising but preliminary signals. Haemoglobin normalisation potentially masking underlying pathologies ("masked anaemia") may warrant specific monitoring.

Conclusions

RWD-based evidence supports progressive repositioning of SGLT2i as systemic endocrine-metabolic agents, with gout and anaemia approaching guideline-level maturity. Methodological evolution towards Target Trial Emulation has strengthened observational inference. Future priorities include multicontinental data integration, standardised lag periods and active comparators, and enhanced clinical vigilance to prevent biochemical improvement from obscuring underlying diagnoses.

1. Introduction

1.1 Background: the evolution of SGLT2 inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors represent a prime example of pharmacological evolution. Originally developed for glycaemic control in type 2 diabetes (T2DM), they are now cornerstones of multisystemic organ protection. Following their initial approval (2013–2014), the EMPA-REG OUTCOME trial (2015) and subsequent large-scale trials (DAPA-CKD, EMPA-KIDNEY) established their efficacy in heart failure and chronic kidney disease, regardless of the presence of diabetes [1–3]. Although current guidelines (ESC, ADA, KDIGO) position them as the standard of care for cardiorenal conditions, the observation of benefits extending beyond these areas suggests an even broader biological versatility [4–6]. The positive development of this class has not been without significant safety concerns – including an increased risk of amputations with canagliflozin (the CANVAS trial) and euglycaemic ketoacidosis – which have helped to define their current risk-benefit profile and necessitate caution when extrapolating evidence to populations not studied in registration trials [7, 8].

1.2 Pleiotropy and Drug Repurposing

The key to the drug repurposing of SGLT2i lies in their pleiotropy, that is, their ability to modulate pathophysiological pathways distinct from glucose inhibition [9]. This process is understood here in the sense defined by Pushpakom et al. (2019) as the identification of new clinical indications independent of the pathophysiological distance from the original indication [10]. The literature identifies three cross-cutting pillars:

1. **Modulation of inflammation:** inhibition of the NLRP3 inflammasome reduces pro-inflammatory cytokines, suggesting applications in gout, COPD and neurodegeneration [11].
2. **Metabolic reprogramming:** the induction of ketone bodies (the ‘super-fuel’ hypothesis) is thought to improve cellular energy efficiency, opening up new frontiers in neuroprotection and oncology [12].
3. **Microvascular protection and erythropoiesis:** the modulation of HIF-2 α factors provides a rational basis for the treatment of anaemia and ischaemic damage [13].

Added to these is the direct uricosuric effect (mediated by interference with the URAT1 and GLUT9 transporters), which is useful in gout and orphan diseases. In this context, glycosuria acts as an amplifier of the uricosuric signal rather than as a primary mechanism [14–16].

1.3 The role of Real-World Data (RWD)

Whilst randomised clinical trials (RCTs) are subject to constraints in terms of cost, duration and restrictive inclusion criteria, Real-World Data (RWD) allows for the observation of real-world populations (the elderly, frail individuals) and rare diseases (e.g. GSD 1b) that would otherwise be difficult to study [17, 18]. The shift towards Target Trial Emulation, supported by advanced statistical techniques (Propensity Score Matching, active comparators), now makes it possible to transform data from clinical practice into reliable comparative efficacy evidence [19, 20]. However, observational evidence requires rigorous management of structural biases such as confounding by indication, immortal time bias and channelling bias, which will be critically analysed in this review [21, 22].

1.4 Aim of the study

Given the rapid accumulation of non-glycaemic evidence on SGLT2i, a systematic synthesis is required to map their overall therapeutic potential. This study aims to analyse the real-world data (RWD)-based literature on the repositioning of SGLT2 inhibitors, pursuing three objectives:

1. **Clinical mapping:** to identify emerging areas (gout, anaemia, COPD, neuroprotection, oncology and rare diseases).
2. **Trend analysis:** to assess the geographical distribution and the role of large international databases (e.g. TriNetX, NHIRD).
3. **Evidence assessment:** to critically examine the methodological quality and maturity of the evidence for each indication.

In summary, the study aims to define the state of the art in the repositioning of SGLT2i, providing a map of the available evidence to guide both clinicians in their daily practice and researchers in planning future studies.

2. Methods

2.1 Search strategy and protocol

This review was conducted in accordance with the PRISMA-ScR guidelines [23]. The study protocol was registered in advance on the Open Science Framework (OSF) platform (10.17605/OSF.IO/794CX). The decision to conduct a scoping review was driven by the need to map a heterogeneous therapeutic landscape, including both large-scale cohort studies and evidence derived from rare diseases.

A systematic search was carried out from the inception of the databases to 31 May 2026 in PubMed and Scopus. The search strategy was designed to cover the domains of SGLT2 inhibitors, real-world data (RWD) and drug repurposing, using MeSH terms and keywords in the title/abstract to ensure maximum sensitivity in record retrieval. The full search strategy is available in Supplementary Material 1.

2.2 Study selection and inclusion criteria

Study selection was guided by the **PCC (Population, Concept, Context)** framework:

- **Population (P):** Patients of all ages, ethnicities and underlying conditions (both diabetic and non-diabetic).
- **Concept (C):** Drug repurposing, pleiotropic effects or new clinical indications for SGLT2i. Studies focusing exclusively on already approved cardio-renal indications and pre-clinical studies (in vitro/animal) were excluded.
- **Context (C):** Studies based on real-world data (cohort studies, case series). Only original peer-reviewed articles were included, excluding grey literature, editorials and conference abstracts.

The selection process was conducted as a double-blind review using the Rayyan QCRI platform. Two reviewers independently assessed titles/abstracts and, subsequently, the full texts. Disagreements were resolved by consensus. Inter-reviewer agreement was high (Cohen's $\kappa = 0.81$). The entire process is summarised in the PRISMA flow chart (Fig. 1).

2.3 Data extraction

Data were extracted by one reviewer and independently verified by a second reviewer using a standardised database. For each study, the following parameters were collected:

1. **Study characteristics:** author, year, geographical area and data source (e.g. TriNetX, NHIRD).
2. **Population and setting:** sample size, comorbidities, repositioning indication under investigation and duration of follow-up.
3. **Statistical methodology:** study design, active comparator, matching techniques (PSM, IPTW) and bias management (lag periods, competitive risks).
4. **Outcomes:** point estimates (HR, OR) or biochemical changes with corresponding confidence intervals (95% CI).

The source of funding and potential conflicts of interest were recorded as contextual factors; the analysis did not identify any systematic distortions in the results linked to industrial support.

2.4 Assessment of Methodological Quality

Methodological rigour was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the tool developed by Murad et al. for case series [24, 25]. The latter was preferred due to its ability to assess biological causality (challenge/re-challenge), a key consideration in drug repositioning. The studies were classified as: High quality (NOS 7–9), Moderate (5–6) or Low (< 5). Detailed scores are provided in Supplementary Material 2.

Given the extreme clinical and methodological heterogeneity, the conduct of a meta-analysis was excluded a priori. The results were summarised narratively through thematic mapping by clinical area (cluster). To illustrate the robustness of the data, a 'Quality of Evidence' matrix (Table 1) was constructed, cross-referencing the volume of studies by indication with their average methodological quality.

3. Results

3.1 Study selection, temporal trends and geographical distribution

The selection process (Fig. 1) resulted in the inclusion of 74 primary studies [32–106] published between 2017 and 31 May 2026. The significant contribution of manual searching (21%, $n = 16$) reflects the intrinsic nature of drug repurposing: signals of efficacy often emerge from secondary or post-hoc analyses not specifically indexed in primary databases. Snowballing was therefore crucial for identifying evidence that would otherwise have remained hidden.

The temporal analysis highlights a gradual increase in scientific output. In the period 2017–2021, 10 studies were identified, characterised by the pioneering role of Real-World Evidence in extending the cardio-renal indications of SGLT2 inhibitors, with initial signals also emerging in the field of gout. From 2023 onwards, a significant increase in output is observed, peaking in the three-year period 2024–2026 with 50 studies (66% of the total). This increase appears to reflect primarily the greater availability and maturity of Real World Data databases and improvements in analytical tools, rather than a simple indexing effect (Fig. 2) [27].

Research appears to be concentrated in Asia and North America (Fig. 3). Asia (27 studies) has established itself as the main ‘global laboratory’ thanks to the centralisation of national databases (e.g. NHIRD), which ensure complete population coverage [28, 29]. North American pragmatism (24 studies), on the other hand, exploits the granularity of EHR networks (e.g. TriNetX) to map detailed laboratory parameters [30]. Europe (16 studies), whilst fragmented, offers diverse clinical contexts (from Scandinavian registries to Central European data flows) that are valuable for the generalisability of the results [31].

3.2 Mapping Clinical Indications: from Chronic Conditions to Rare Niche Conditions

Analysis of the 74 studies has enabled us to map a vast therapeutic landscape, which we have divided into clusters according to clinical and numerical relevance.

Table 1

Study quality matrix. Thematic mapping by clinical area, study volume and methodological rigour. The review identified a further 11 studies not included in the matrix: 6 historical studies and 5 exploratory studies aimed at generating hypotheses (Section 3.4.5) [95–105].

Clinical Area	No. of Studies	Key Findings**	Average Quality
Gout [32–50]	19	Risk reduction 30–50%	⊠⊠⊠ (NOS median: 7 [4–9])
Anaemia [51–60]	10	Increase in Hb + 0.7/1.0 g/dL	⊠⊠⊠ (NOS median: 5.5 [3–8])
COPD [61–69]	9	Risk reduction 19–38%	⊠⊠⊠ (NOS median: 5 [3–8])
Rare Diseases [70–82]	13	Clinical metabolic impact	⊠⊠⊠ (Murad median: 7 [5–7])*
Neuroprotection [83–86]	4	Reduction in the incidence of dementia	⊠⊠⊠ (NOS median: 7 [7–8])
Hepatoprotection [87–91]	5	Reduction in ascites decompensation	⊠⊠⊠ (NOS median: 6 [5–9])
Oncology [92–94]	3	Reduction in incidence/mortality	⊠⊠⊠ (Median NOS: 7 [5–8])

*Assessment conducted using the tool developed by Murad et al. (2018), specifically designed for case series in orphan populations.

**The values reported represent the ranges of the point estimates from the included studies. Detailed data on confidence intervals and the reference list are provided in Section 3.4 and in Supplementary Material 3.

3.3 Methodological Synthesis: The Evolution Towards Target Trial Emulation

The analysis of methodological quality highlights a clear trend towards Target Trial Emulation. The majority of studies classified as “High” in quality adopt a New-User Active-Comparator design. The most frequently used active comparators are DPP-4 inhibitors and GLP-1 receptor agonists, whilst older-generation drugs (metformin or sulphonylureas) appear to be less well represented.

As regards group balancing, 1:1 or 1:n Propensity Score Matching (PSM) is the standard technique. However, in the most recent two-year period (2025–2026), there has been an increase in the use of IPTW and Sequence Symmetry Analysis (SSA), the latter being used in five studies to establish the temporal sequence between the start of treatment and the event. Finally, the use of lag periods (1–2 years) is mainly confined to oncology and neuroprotection studies. Although their application is frequent in these

fields, the analysis reveals considerable heterogeneity in the choice of lag period duration, often not supported by specific sensitivity analyses.

Quality Distribution by Area:

3.3.1 High-quality areas: Gout, Neuroprotection and Oncology

The gout area represents the most robust part of the review, with a total of 19 studies and a prevalence of medium-to-high-quality studies. The robustness of the results is supported by the widespread adoption of Target Trial Emulation approaches, primarily via 1:1 propensity score matching (10 studies) and within-patient designs (5). In particular, the use of Sequence Symmetry Analysis in 5 studies helped to strengthen the temporal validity of the associations. Overall, these approaches have enabled a comparison between SGLT2i and other modern antidiabetic drugs (DPP-4i and GLP-1 RA), highlighting consistent evidence of benefit in reducing acute clinical events.

The field of neuroprotection, aimed at preventing Alzheimer's disease and stroke, and the field of oncology, focused on long-term survival outcomes (5–6 years), are characterised by a generally high standard of quality. This robustness is underpinned by the application of rigorous protocols for controlling confounders and the use of lag periods, aimed at reducing protopathic bias in chronic and progressively evolving conditions. However, in both fields, the studies are still at a preliminary stage.

3.3.2 'Average Quality' and the Limits of Granularity: Anaemia, COPD and Hepatoprotection

Anaemia is investigated not only in terms of improvements in haematological parameters, but also with a view to reducing the pharmacological burden, particularly that of erythropoiesis-stimulating agents (ESAs). The availability of granular databases, such as EHRs and integrated medical records, allows for the direct analysis of haemoglobin (Hb) levels, providing useful information for assessing the potential therapeutic repositioning of SGLT2i. However, the average methodological quality of the studies is limited by their frequent single-centre nature and small sample sizes, as seen in the studies by Yoshida and Ziyadanoğlu [52, 60]. Added to this is the use of self-controlled before-and-after designs or the absence of an active control group, factors which reduce internal validity.

COPD and liver protection emerge as areas of interest regarding the potential role of SGLT2 inhibitors in the management of patients with multiple comorbidities. In these clusters, studies rely predominantly on large-scale, often national, administrative databases, which ensure high sample sizes and good representativeness, but are limited by the scarcity of clinical variables relevant for controlling confounders. The difficulty in accurately identifying complex outcomes, such as respiratory exacerbations or ascites decompensation, together with the lack of information on key factors such as smoking status, cirrhosis staging or dietary variables, limits risk stratification. Consequently, despite the consistency of the results and the size of the cohorts, the overall level of evidence remains moderate.

3.3.3 The ‘Rare Disease Paradox’: between formal rigour and intrinsic limitations

The cluster of rare and orphan diseases comprises 13 studies characterised by high pathophysiological heterogeneity, ranging from type 1b glycogen storage disease to Ménière’s disease. In this context, real-world data takes on ethical significance, as it often represents the only available source of evidence to support access to therapies in the absence of clinical trials.

From a methodological perspective, a distinction must be made between the different conditions. In sarcoidosis, the relatively large sample size in large-scale databases (e.g. TriNetX) has allowed the application of the Newcastle-Ottawa Scale, yielding results of good overall quality. Conversely, for ultra-rare diseases (GSD 1b, Ménière’s disease, cystinuria), the evidence consists mainly of case series assessed using the tool developed by Murad et al., with generally high scores in terms of descriptive accuracy, except for one case of ‘average’ quality (Grunert 2024) due to the use of telephone interviews, which is associated with possible reporting bias [76].

Despite the generally favourable methodological scores, the evidence in the orphan disease field has significant limitations, including potential publication bias and the inability to completely isolate the effect of treatment from confounding factors, such as concomitant changes in clinical follow-up or dietary management.

3.4 Analysis by Area

3.4.1 Established evidence: SGLT2i and gout

The efficacy of SGLT2i repurposing in gout is documented across three main dimensions. From a biochemical perspective, a reduction in serum uric acid (SUA) of between 0.5 and 0.9 mg/dL is observed, with the uricosuric effect persisting even in patients with heart failure, although it is attenuated in those with an eGFR < 60 mL/min [40, 46]. Clinically, the use of SGLT2i is associated with a 30–50% reduction in the risk of new-onset gout and a 33–34% reduction in flares and emergency hospital admissions [32, 33, 38, 41]. From a therapeutic perspective, a drug-sparing effect is observed, with a 38% reduction in the initiation of allopurinol and reduced use of NSAIDs and high-dose glucocorticoids [47].

Comparison with standard therapies reveals further promising findings. In particular, compared with allopurinol, SGLT2 inhibitors are associated with greater stability in renal function at 36 months and lower mortality, against a background of progressive decline in glomerular filtration rate observed with conventional therapy [49]. Similar findings also emerge when compared with GLP-1 RAs, suggesting a specific uricosuric effect distinct from general metabolic improvement [32, 33].

3.4.2 Systemic impact (anaemia): Clinical benefits versus risks (masked anaemia).

The repositioning of SGLT2i in the context of anaemia is based on evidence that the increase in haematological parameters is not attributable solely to a haemoconcentration effect. Ziyadanoğlu's study, through the analysis of extracellular fluid (ECF) volumes, suggests that the increase in haemoglobin is not solely related to fluid reduction [60]. Similarly, Murashima reports an increase in mean corpuscular volume (MCV), consistent with genuine erythrocyte expansion and a possible effect on endogenous erythropoietin production [59].

The clinical benefit of repositioning is also evident from the 'major' outcomes reported in RWD. Steinmetz documents a 64% reduction in the use of erythropoiesis-stimulating agents (ESAs), whilst a hazard ratio of 0.67 for hospitalisations related to anaemia suggests a reduction in acute clinical events [57].

One aspect of particular relevance is the phenomenon of 'masked anaemia' described by Schwarz et al. in a cohort of 9,646 patients with type 2 diabetes. In 15.5% of cases (n = 1,215), patients who were anaemic at baseline showed normalisation of haemoglobin levels following treatment with SGLT2i [54]. Although this normalisation represents a favourable outcome, the authors highlight the potential risk of masking underlying conditions, such as chronic gastrointestinal bleeding or early-stage neoplasms, with possible diagnostic delay if further clinical investigations are not carried out.

3.4.3 New frontiers (COPD, neurology, liver): Analysis of signals of superiority.

The new frontiers in the repositioning of SGLT2i include COPD, neuroprotection and liver diseases, with evidence that remains mixed but is steadily expanding.

In COPD, the main finding concerns the reduction in severe exacerbations (19–38%). Although no clear superiority over GLP-1 RAs has been demonstrated, SGLT2i appear to offer a potential benefit in patients with multiple comorbidities due to the concurrent management of cardiovascular and respiratory risk [66, 67].

In the neuroprotective context, studies by Kim and Zhou report associations between the use of SGLT2i and a reduced risk of Alzheimer's disease and vascular dementia compared with metformin and GLP-1 Ras [85, 86]. A 30% reduction in the risk of ischaemic stroke compared with metformin has also been observed, suggesting a possible effect on cerebral microcirculation. However, the limited number of studies and the long latency period of neurodegenerative diseases require confirmation through longer-term follow-up.

With regard to hepatoprotection, the evidence has evolved from a demonstration of safety in patients with cirrhosis to indications of an improvement in hepatic steatosis. Studies based on the Fatty Liver Index (FLI) indicate a greater reduction in intrahepatic fat accumulation compared with DPP-4 inhibitors [90]. Furthermore, Abu-Hammour suggests a possible synergistic effect with traditional diuretics (furosemide) in preventing ascites decompensation in patients with cirrhosis [91].

3.4.4 The Value of RWD in Rare Diseases: Bridging the Gap Left by Clinical Trials.

In rare diseases, Real-World Data has contributed significantly to the development of new therapeutic strategies, bridging the gap left by the absence of controlled clinical trials.

In type 1b glycogen storage disease and Fanconi-Bickel syndrome, studies have confirmed the role of SGLT2 inhibitors in reducing the accumulation of 1,5-anhydroglucitol, a toxic metabolite associated with neutrophil dysfunction and renal tubular damage [73]. Studies conducted in national settings such as China and Turkey report a reduction in infections and the use of G-CSF, as well as an improvement in symptoms associated with inflammatory bowel disease in GSD 1b [74, 75] .

In paediatrics, the role of real-world data (RWD) is particularly evident in vulnerable populations excluded from registration trials. The review identified an international case series of 21 infants with GSD 1b treated with empagliflozin off-label [76]. In this real-world practice setting, treatment was initiated early (median 20 days of life) at a dose of 0.3 mg/kg/day. With a median follow-up of 12.1 months, no serious adverse events were reported, and glycaemic stability was observed in 81% of cases, suggesting the feasibility of early repositioning under clinical supervision.

3.4.5 Historical and exploratory studies: How RWD has anticipated (and will anticipate) clinical trials.

Finally, analysis of historical studies (2017–2020) highlights the ability of Real-World Data to anticipate certain findings subsequently confirmed by randomised clinical trials. Studies such as CVD-REAL Nordic and Pasternak's work had, in fact, documented signs of renal and cardiovascular protection in real-world clinical practice settings prior to the publication of the DAPA-CKD and EMPA-KIDNEY trials [95, 99].

This context also includes studies on type 1 diabetes (T1DM), a historically controversial indication that was subsequently restricted due to the risk of diabetic ketoacidosis (DKA). The analyses by Pandey et al. and Edwards et al. suggest that, in real-world clinical practice, the risk of DKA is not increased compared with controls, whilst evidence of benefit persists regarding major adverse cardiovascular events (MACE), glycaemic control and patient-reported quality of life [101, 102].

Looking ahead, the work of Tan et al. points to the usefulness of agnostic screening approaches (outcome-wide analyses) for identifying new signals of efficacy, including anaemia, COPD and possible associations with bladder and pancreatic cancers, as well as preliminary signals in inflammatory bowel diseases [103–105]. These findings suggest potential avenues for future repositioning hypotheses.

4. Discussion

4.1 Methodological evolution: from validation to Target Trial Emulation

The evolution of research based on Real-World Data (RWD) on SGLT2 inhibitors highlights a progressive methodological maturation, accompanied by a growing heterogeneity of approaches depending on clinical objectives. Historical studies (2017–2021), such as CVD-REAL and Ueda's work, have helped to define standards of statistical rigour across large populations, supporting the validation of cardio-renal evidence in real-life settings compared with registration trials. In contrast, more recent research (2024–2026) shows greater diversification, with the adoption of Target Trial Emulation in the neuroprotective field and an increase in studies in niche areas or rare diseases, where smaller sample sizes and fragmented databases account more for qualitative variability than for any real methodological weakness.

A key element of this evolution is the widespread adoption of the New-User Active-Comparator design, which helps to reduce systematic biases such as healthy user bias and channelling bias through comparison with contemporary active therapies (DPP-4i and GLP-1 RA). This is complemented by more rigorous management of the index date, the use of competitive risk models (Fine-Gray) and balancing techniques such as propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). Sequence symmetry analysis (SSA) and the use of lag periods have further contributed, in some studies, to strengthening temporal consistency and reducing reverse causality bias and protopathic bias, although their application is not yet uniform and dedicated sensitivity analyses are often lacking. Finally, tools such as negative control outcomes and E-values have enabled the estimation of residual confounding, thereby strengthening causal inference in observational analyses.

At the same time, there is a clear prevalence of studies on empagliflozin and dapagliflozin, likely linked to their longer time on the market and the availability of longer follow-up periods, rather than to intrinsic differences in pleiotropic efficacy. The lower representation of canagliflozin and ertugliflozin, as well as the absence of robust data for more recently introduced molecules, reflects the natural delay in the accumulation of post-marketing evidence. The question of the generalisability of class effects remains open, with a future need to investigate any differences linked to SGLT1/2 selectivity or the pharmacokinetic profiles of individual molecules.

Overall, this development has progressively transformed RWD from a descriptive tool into a platform for experimental emulation, providing more structured support for the repositioning of SGLT2i based on comparative evidence.

4.2 Cross-Cutting Pleiotropic Mechanisms: clinical validation of biological hypotheses

The broad spectrum of efficacy observed suggests that SGLT2 inhibitors may act as systemic modulators of shared pathophysiological pathways. Real-world data support three main mechanistic

axes.

1. **1. Inhibition of the NLRP3 inflammasome:** The most consistent signal emerges in gout, COPD and neurodegeneration. In gout, the reduction in flares (33–34%) and the sparing of corticosteroids suggest a possible role for the suppression of the IL-1 β cascade. This anti-inflammatory profile is consistent with the reduction in respiratory exacerbations and with the signs of cognitive protection reported in clinical practice.
2. **2. Haemodynamic and microvascular stability:** In the management of Ménière's disease and liver disease, SGLT2 inhibitors are associated with a modulation of organ pressures (the 'hydraulic' effect). Furthermore, signals protecting the microcirculation may contribute to the associations with reduced ischaemic stroke and cognitive decline observed in the studies by Kim and Zhou, regardless of glycaemic control [85, 86].
3. **3. Metabolic clearance and nutrient sensing:** In rare diseases (GSD 1b and Fanconi-Bickel syndrome), real-world data (RWD) support the role of 1,5-anhydroglucitol as a toxic metabolite, with SGLT2 inhibitors facilitating its renal clearance. In oncology, observational data suggest possible modulation of the insulin/IGF-1 axis, consistent with the hypothesis of tumour nutrient deprivation [92, 94].

Finally, in anaemia, the increase in haemoglobin appears more consistent with an effect on erythropoiesis than with simple haemoconcentration, as suggested by the rise in MCV and the reduced use of ESAs. This effect has been interpreted as potentially mediated by reduced tubular stress and changes in the hepcidin axis, although the mechanisms remain to be clarified.

4.3 Outstanding Challenges and 'Blind Spots' in Real-World Data

In line with the mapping objectives inherent to a scoping review, the heterogeneity of the association metrics used (HR, RR, SR), the inclusion of cohorts with varying methodological maturity, and the variability in follow-up periods should not be interpreted as shortcomings of the review, but rather as an accurate representation of the differing degrees of progress in therapeutic repositioning across various clinical areas. Indeed, highly heterogeneous trajectories emerge, ranging from early exploratory signals observed over short time frames – typical of emerging indications such as COPD and anaemia – to the more rigorous long-term trial emulations, now well-established in the case of gout.

The use of Real-World Data, however, has inherent limitations that define the boundaries of the evidence currently available. Although Target Trial Emulation represents a significant methodological advance, it cannot compensate for the absence of key clinical variables in administrative databases. In COPD, for example, smoking remains a major residual confounder, often managed through indirect proxies. Similarly, in studies on anaemia, a significant qualitative difference emerges between insurance databases based on ICD codes and Electronic Health Records (EHRs), which instead provide access to actual haematological parameters, such as haemoglobin levels. This highlights the need for future integration between different data streams.

A further limitation concerns the clinical interpretation of the results. The phenomenon of ‘masked anaemia’, described by Schwarz, suggests that improvements in haematological parameters may introduce a potential diagnostic bias, masking underlying conditions — such as occult bleeding — and therefore requiring greater attention in clinical practice [54].

In terms of external validity, the generalisability of the results is limited by the geographical fragmentation of the cohorts and by possible healthy user bias. Patients treated with SGLT2i frequently exhibit greater treatment adherence and a more structured clinical follow-up, creating a residual confounder that cannot be fully eliminated even through propensity score matching. This calls for caution when extrapolating the results to different populations, including European cohorts or patients with rare diseases.

Finally, rare diseases present a genuine methodological paradox. Although characterised by small sample sizes and evidence often considered weak by traditional criteria, studies on GSD1b and Fanconi-Bickel syndrome demonstrate the unique value of real-world data in these contexts. In the absence of randomised clinical trials, observational evidence becomes the main available source, and may also play a potential role in ensuring equity of access to treatments.

4.4 Clinical and Regulatory Implications: towards a Multisystemic Approach to Medicine

The repositioning of SGLT2 inhibitors through Real-World Data represents a potential driver of change for clinical practice and healthcare policy.

Areas such as gout and anaemia show signs of maturity suggesting a possible more structured integration into clinical guidelines. In these contexts, SGLT2 inhibitors could help simplify treatment for patients with complex diabetes, reducing the need for allopurinol, ESAs and intravenous iron therapy, as well as having a favourable impact on adherence and the risk of drug interactions.

From a healthcare systems perspective, real-world data support assessments of economic sustainability. The reduction in hospitalisations (HR 0.67 for anaemia) and acute events in gout suggests a possible shift towards value-based healthcare models, in which the cost of treatment is interpreted in relation to the prevention of clinical events.

In the regulatory sphere, type 1 diabetes represents a paradigmatic case of tension between real-world evidence and regulatory restrictions linked to the risk of ketoacidosis. Observational data indicate off-label use driven by perceived benefits to quality of life, suggesting a possible need for more flexible regulatory pathways and dedicated monitoring protocols.

Finally, in ultra-rare diseases, Real World Data plays a central role in the absence of clinical trials. In these contexts, observational evidence often represents the only available basis for supporting therapeutic decisions and access to treatments, helping to reduce inequalities in access to care.

5. Conclusions

This review highlights how the repositioning of SGLT2 inhibitors (SGLT2i), guided by Real World Data, demonstrates a progressive expansion of their role from hypoglycaemic agents to drugs with potential multisystemic action. The 74 included studies identify stronger signals in areas such as gout and anaemia, whilst neuroprotection, hepatoprotection and oncology remain promising but still preliminary areas, requiring confirmation through longer follow-up periods and more heterogeneous populations.

From a methodological perspective, observational research is evolving towards more rigorous approaches, particularly through Target Trial Emulation, which has enhanced the ability of real-world data to support therapeutic comparisons in clinical practice. In the context of rare diseases and vulnerable populations, such data often represent the only available source in the absence of controlled trials. In this scenario, SGLT2i are situated within a context of increasing multimorbidity, with potentially concomitant effects on inflammatory, metabolic and haemodynamic pathways.

Future research directions include the standardisation of study designs through the use of active comparators and lag periods, the integration of multinational databases to increase generalisability, and the strengthening of clinical vigilance to reduce the risk of misleading interpretations of biochemical improvements.

In summary, SGLT2i represent an example of drug repositioning guided by real-world data, with a progressive expansion of their clinical role beyond glycaemic control.

Limitations

It cannot be ruled out that the marked increase in output during the three-year period 2024–2026 may partly reflect a positive publication bias, whereby studies with negative or null signals remain unpublished, thereby amplifying the perception of the pleiotropic efficacy of SGLT2i in the most methodologically heterogeneous areas.

Abbreviations

SGLT2i

Sodium/glucose cotransporter-2 inhibitors

RWD

Real World Data

T2DM

Type 2 diabetes mellitus

GLUT

Glucose transporter

DKA

Diabetic Ketoacidosis

ECF
Extracellular Fluid
ESA
Erythropoiesis-Stimulating Agents
FLI
Fatty Liver Index
MACE
Major Adverse Cardiovascular Events
MCV
Mean Corpuscular Volume
SSA
Sequence Symmetry Analysis

Declarations

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Figures

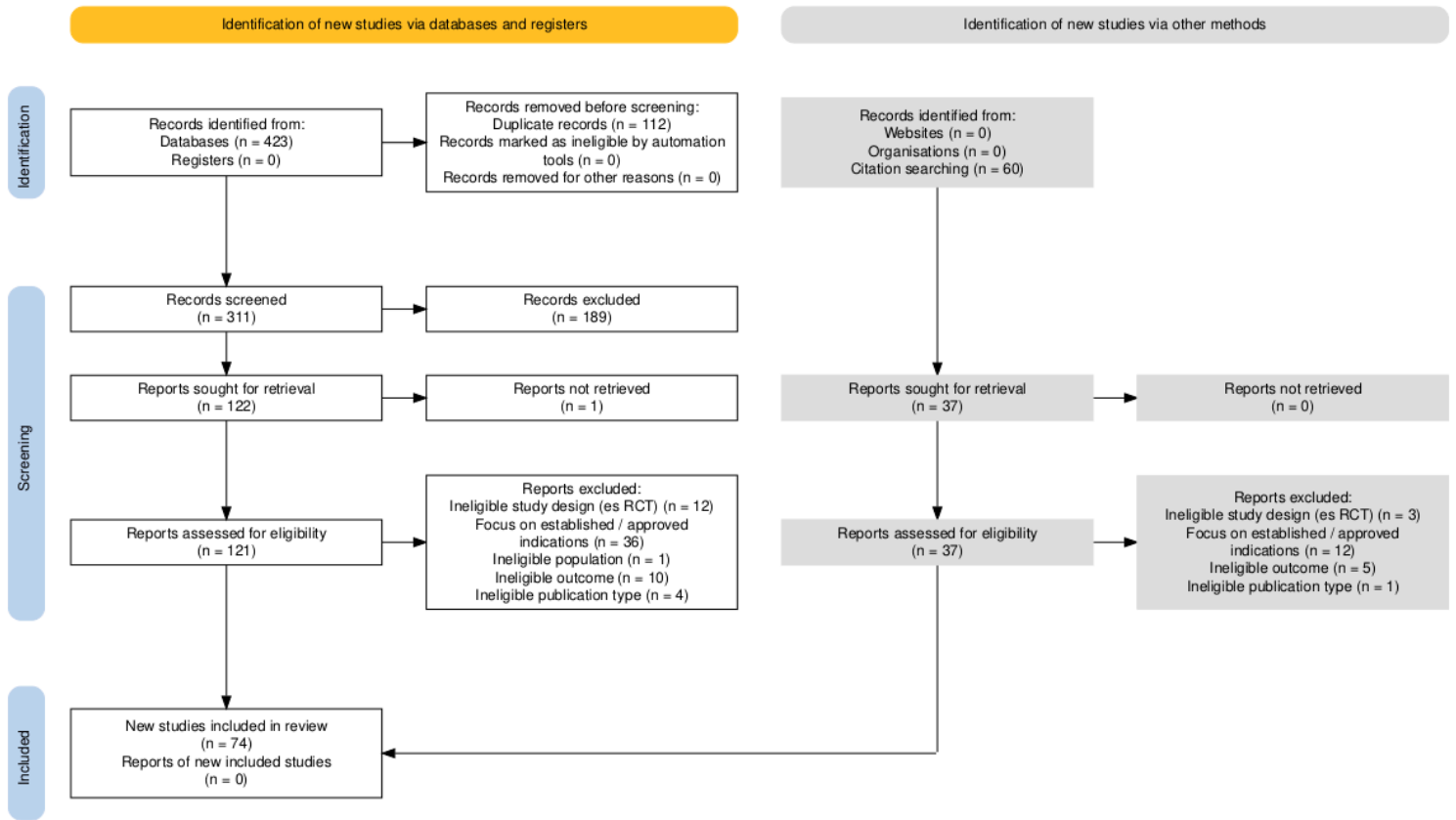


Figure 1

PRISMA 2020 flowchart relating to the study selection process, generated using the Shiny PRISMA2020 application (Haddaway et al., 2022) [26].

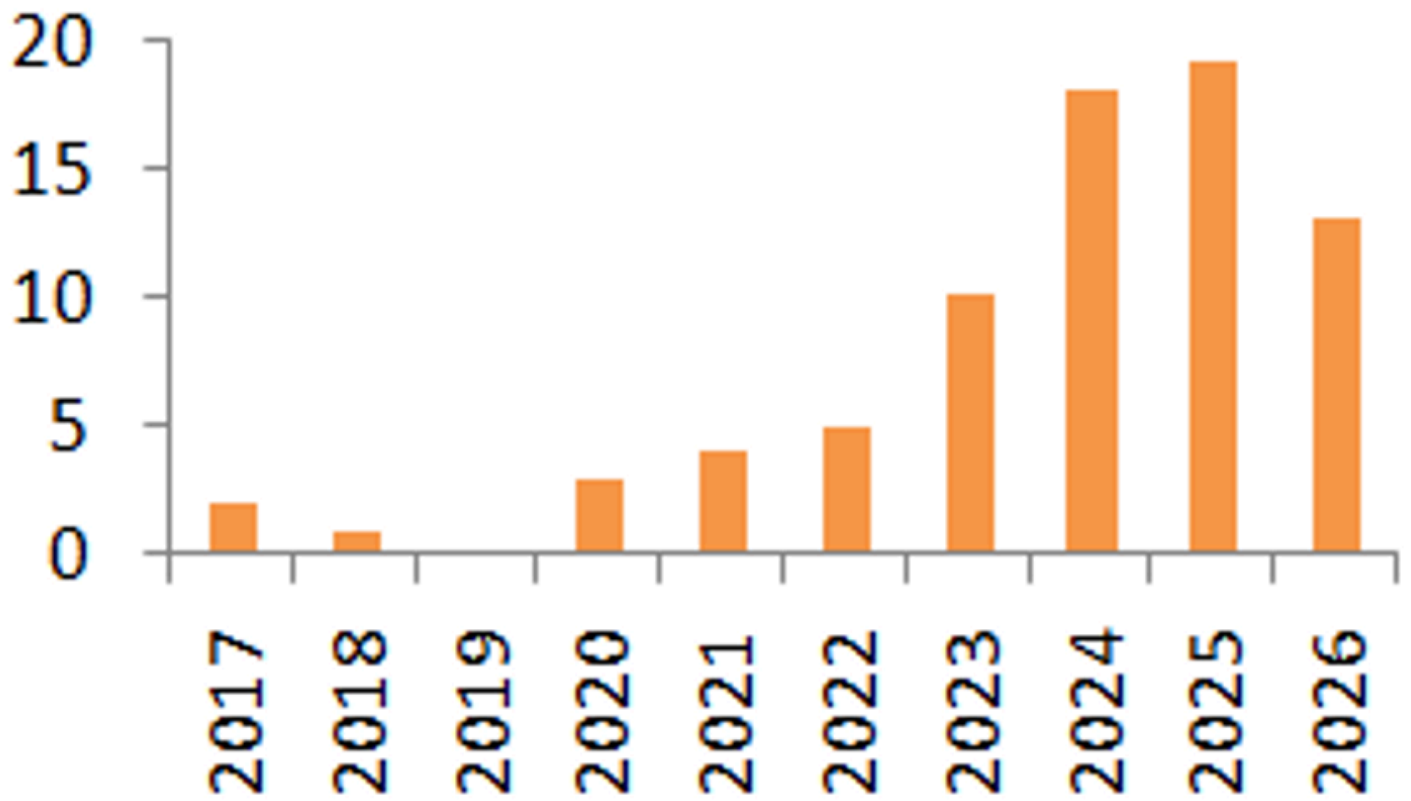
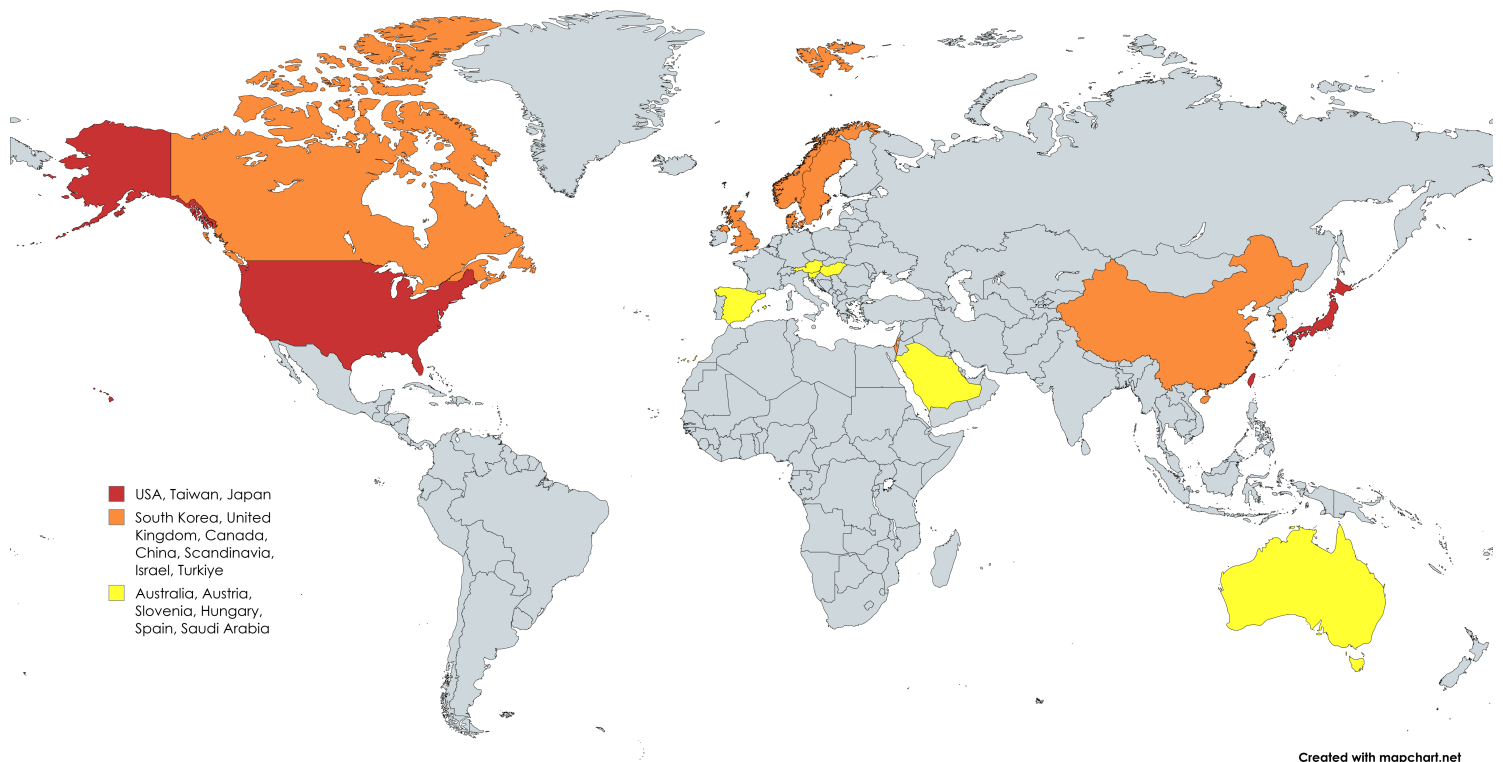


Figure 2

Temporal distribution of the studies considered



Created with mapchart.net

Figure 3

Global geographical distribution of the included studies. The heatmap indicates the frequency of publications by country of origin of the database. Darker colours indicate a higher density of research (peaks in the USA, Taiwan and South Korea). Note: 6 international multi-database studies are not colour-coded on the map.

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- [SupplementaryMaterial2.xlsx](#)
- [SupplementaryMaterial3.xlsx](#)
- [GraphicalAbstract.jpg](#)