# research

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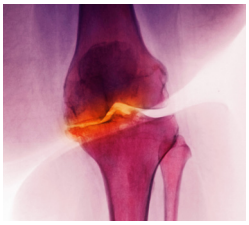

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**ORIGINAL RESEARCH** Natural experiment study

## Exposure to sugar rationing in first 1000 days after conception and long term cardiovascular outcomes

Zheng J, Zhou Z, Huang J, et al

**Cite this as:** *BMJ* 2025;391:e083890
Find this at doi: 10.1136/bmj-2024-083890

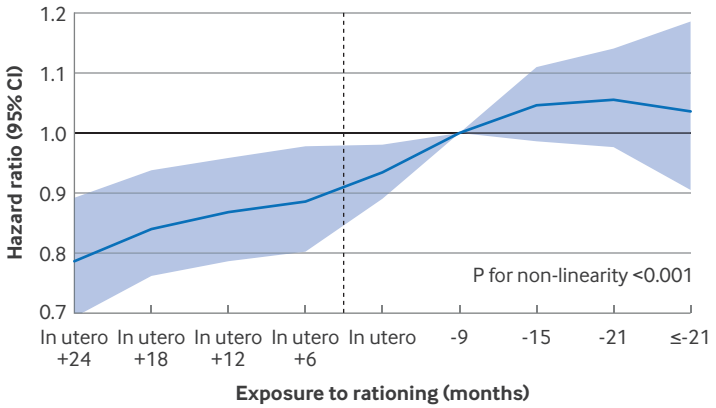
**Study question** Is exposure to sugar rationing during the first 1000 days after conception associated with a reduced risk of cardiovascular disease in adulthood?

**Methods** A natural experiment based on the UK's sugar rationing policy was used to assess the long term effects of restricted sugar intake during early life. UK Biobank participants born between October 1951 and March 1956 were grouped by early life exposure to sugar rationing. Cox and parametric hazard models adjusted for demographic, socioeconomic, lifestyle, and genetic factors were used to compare major cardiovascular outcomes—cardiovascular disease, myocardial infarction, heart failure, atrial fibrillation, stroke, and cardiovascular mortality—between groups. Mediation by diabetes, hypertension, and birth weight was also assessed.

**Study answer and limitations**
Sugar rationing during early life was associated with lower risks of several cardiovascular outcomes in adulthood. Compared with people never exposed to rationing, those exposed in utero plus one to two years had hazard ratios of 0.80 (95% confidence interval 0.73 to 0.90) for cardiovascular disease, 0.75 (0.63 to 0.90) for myocardial infarction, 0.74 (0.59 to 0.95) for heart failure, 0.76 (0.66 to 0.92) for atrial fibrillation, 0.69 (0.53 to 0.89) for stroke, and 0.73 (0.54 to 0.98) for cardiovascular disease mortality. Incident diabetes and hypertension jointly mediated 31.1% of the sugar rationing-cardiovascular disease association. Limitations include absence of detailed individual dietary data and potential recall bias.

**What this study adds** Sugar rationing during the first 1000 days after conception is linked to lasting cardiovascular benefits in adulthood. The findings reinforce recommendations to minimise added sugars in the diets of infants and pregnant women.

**Funding, competing interests, and data sharing** Funded by the Guangzhou Municipal Research Fund. No competing interests declared. Data from UK Biobank are available on reasonable request.




Hazard ratios for different cardiovascular outcomes by various levels of exposure to sugar rationing. Vertical broken line indicates end of sugar rationing. CI=confidence interval

# SGLT-2 inhibitors for the prevention of autoimmune rheumatic diseases

**ORIGINAL RESEARCH** Population based cohort study

## Sodium-glucose cotransporter-2 inhibitors and risk of autoimmune rheumatic diseases

Hong B, Lee H, Jung K, Rhee SY, Yon DK, Shin J-Y

**Cite this as:** *BMJ* 2025;391:e085196
Find this at doi: 10.1136/bmj-2025-085196

**Study question** Do sodium-glucose cotransporter-2 (SGLT-2) inhibitors reduce the risk of autoimmune rheumatic diseases in adults with type 2 diabetes compared with sulfonylureas?

**Methods** This population based retrospective cohort study used nationwide healthcare data from South Korea from 2012 to 2022. Adults with type 2 diabetes who initiated either SGLT-2 inhibitors or sulfonylureas were included. The primary outcome was the development of an autoimmune rheumatic disease. Inverse probability treatment weighting based on propensity scores was applied to normalise baseline characteristics. Hazard ratios and rate differences per 100 000 person years were estimated.

**Study answer and limitations** After propensity score weighting, 1 030 088 initiators of SGLT-2 inhibitors (mean age 58.5 years; 59.9% men) and 1 002 069 initiators of sulfonylureas (mean age 58.5 years; 60.1% men) were included in the analysis. The weighted incidence rate per 100 000 person years was 51.90 and 58.41 in individuals initiating SGLT-2 inhibitors and sulfonylureas, respectively. Over a median of nine months' follow-up, SGLT-2 inhibitors were associated with an

**COMMENTARY** Emerging clinical evidence supporting an immunomodulatory effect

The use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors in clinical practice has increased as the multisystem benefits of this drug class have been discovered.[1 2] Beyond improving glycaemic control, these agents are cardioprotective (reduce the risk of major adverse cardiovascular events and hospital admissions for heart failure) and nephroprotective (reduce renal progression in people with chronic kidney disease).[3] Furthermore, they induce modest weight loss (~2% more than placebo) and have been found to have beneficial immunomodulatory effects in preclinical studies.[4] Recent large observational studies have shown that the use of SGLT-2 inhibitors is associated with better cardiac and renal outcomes in people with systemic lupus erythematosus, but this drug class's role in the prevention and treatment of autoimmune rheumatic diseases remains understudied.[4-6]

The study by Hong and colleagues fills an important knowledge gap.[7] The authors performed a population based new user cohort study using a South Korean nationwide health insurance database to evaluate the risk of incident autoimmune rheumatic diseases in adults with type 2 diabetes who initiated SGLT-2 inhibitors. New users of sulfonylureas served as active comparators since sulfonylureas were not expected to affect the risk of autoimmune rheumatic diseases.[8] In exploratory analyses, the effect of SGLT-2 inhibitors on risk of autoimmune rheumatic diseases relative to dipeptidyl peptidase-4 inhibitors, thiazolidinediones, and glucagon-like peptide-1 (GLP-1) receptor agonists was also assessed. The primary outcome, incident autoimmune rheumatic disease (a composite of inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, or spondyloarthritis) and systemic autoimmune rheumatic diseases (systemic lupus erythematosus, Sjögren's disease, systemic sclerosis, idiopathic inflammatory myositis, mixed connective tissue disease, polymyalgia rheumatica, or vasculitides)), was defined using both an ICD-10 (international classification of diseases, 10th revision) code and registration in a national programme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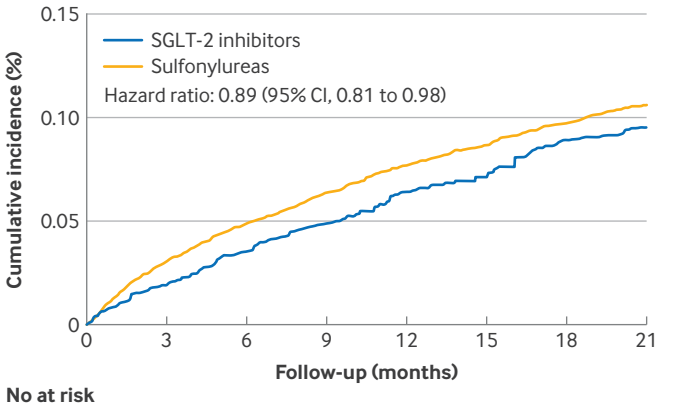



**No at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SGLT-2 inhibitors | 1 030 088 | 817 314 | 629 230 | 519 051 | 446 256 | 388 418 | 342 879 | 303 517 |
| Sulfonylureas | 1 002 069 | 757 720 | 564 973 | 463 980 | 396 867 | 348 555 | 309 925 | 276 246 |

**Cumulative incidence curves of autoimmune rheumatic diseases comparing sodium-glucose cotransporter-2 (SGLT-2) inhibitors with sulfonylureas**


11% lower risk of incident autoimmune rheumatic diseases compared with sulfonylureas (hazard ratio 0.89 (95% confidence interval (CI) 0.81 to 0.98); rate difference −6.50 (95% CI −11.86 to −1.14) per 100 000 person years). As this was an observational study, residual confounding is possible.

**What this study adds** Use of SGLT-2 inhibitors in adults with type 2 diabetes was associated with an 11% lower risk of autoimmune rheumatic diseases compared with use of sulfonylureas.

**Funding, competing interests, and data sharing** This research was supported by the Ministry of Food and Drug Safety, Korea. See full paper on bmj.com for competing interests. Data used for this research are available upon reasonable request and with permission from the data provider.

that required a documented physician assessment confirming the diagnosis of an autoimmune rheumatic disease according to established classification criteria. This was one of the study's strengths. Furthermore, normalised inverse probability of treatment weighting was used to control for potential confounders, and several sensitivity analyses were performed to test the robustness of the findings under different assumptions. Additional strengths included the consideration of time varying confounding and informative censoring, and the inclusion of both a positive and a negative control outcome.

Among 2 032 157 adults with type 2 diabetes followed for a median of nine months, the authors found that new users of SGLT-2 inhibitors had an 11% lower risk of incident autoimmune rheumatic disease compared with new users of sulfonylureas. The rate difference was −6.5 diagnoses per 100 000 person years, yielding a number needed to treat of 15 385. Results were directionally consistent across subgroup and sensitivity analyses. Analyses stratified by type of autoimmune rheumatic disease showed that SGLT-2 inhibitors were associated with a significantly lower risk of inflammatory arthritis, but not systemic autoimmune rheumatic diseases.

### Immunomodulatory effects

Mechanistically, it is biologically plausible that SGLT-2 inhibitors might reduce the risk of autoimmune rheumatic diseases. In preclinical studies, they have been shown to attenuate secretion of key pro-inflammatory cytokines implicated in the pathogenesis of several autoimmune rheumatic diseases, and induce shifts in macrophages from pro-inflammatory M1 to anti-inflammatory M2 subtypes.[9 10] Autoimmune rheumatic diseases are relatively rare diagnoses, however, and incidence rates in Hong and colleagues' study were lower than previous estimates from Sweden and the US.[11 12] Because the outcomes studied were rare, the absolute risk differences were small and the numbers needed to treat were large. The practical implications of the findings must be interpreted with this lens. To prevent one autoimmune rheumatic disease, >15 000 adults with type 2 diabetes would need to be treated with an SGLT-2 inhibitor rather than a sulfonylurea for one year.

**It is biologically plausible that SGLT-2 inhibitors might reduce the risk of autoimmune rheumatic diseases**

While in isolation this study is unlikely to change practice, it is the first full length publication to suggest that SGLT-2 inhibitors reduce the risk of autoimmune rheumatic diseases. This intriguing finding, seen after only nine months of median follow-up, suggests a clinically relevant immunomodulatory effect that warrants replication in different populations. Studies assessing how the effect might change with longer term use and follow-up are awaited.

### Favouring SGLT-2 inhibitors

Finally, a shift away from sulfonylureas and towards SGLT-2 inhibitors and GLP-1 receptor agonists as second line treatment for type 2 diabetes is under way, since both are cardioprotective and nephroprotective and facilitate weight loss, whereas sulfonylureas promote weight gain and carry higher risk of hypoglycaemia.[3] These shifts in practice patterns are seen in table 1 of Hong and colleagues' study as well as in other studies.[1 2] Like SGLT-2 inhibitors, GLP-1 receptor agonists have beneficial immunomodulatory properties, and their role in the prevention and/or management of autoimmune rheumatic diseases similarly warrants further study.[4 13] Exploratory analysis from Hong and colleagues' study suggested that SGLT-2 inhibitors did not reduce the risk of autoimmune rheumatic diseases compared with GLP-1 receptor agonists, but GLP-1 receptor agonists were infrequently used. Whether GLP-1 receptor agonists might also reduce the risk of autoimmune rheumatic diseases remains unknown. Hong and colleagues' study sets a foundation for future research and provides preliminary evidence to support an additional reason to use an SGLT-2 inhibitor over a sulfonylurea for the management of type 2 diabetes.

**Cite this as:** *BMJ* 2025;391:r2121

Find the full version with references at http://dx.doi.org/10.1136/bmj.r2121

# Early findings on the impact of Medicaid work requirements

**ORIGINAL RESEARCH** Quasi-experimental difference-in-differences study

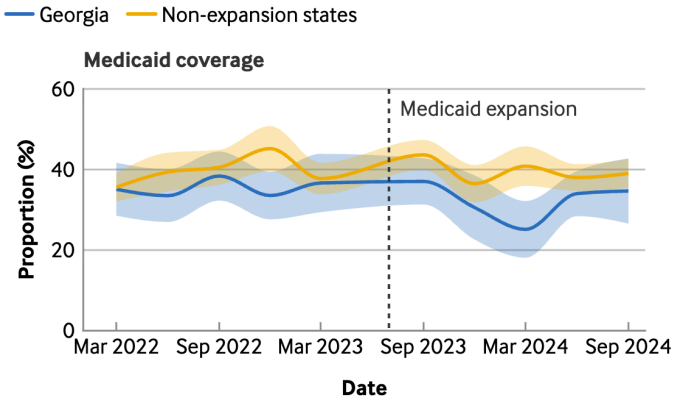
## Insurance coverage and employment after Medicaid expansion with work requirements

Johnson DY, Mein SA, Marinacci LX, et al

Cite this as: *BMJ* 2025;390:e086792
Find this at doi: 10.1136/bmj-2025-086792

**Study question** How did insurance coverage and employment change among working age adults with low incomes in Georgia, the first US state to implement Medicaid expansion with work requirements under the Pathways to Coverage programme?

**Methods** The study population consisted of adults aged 19-64 years with low incomes—defined as ≤100% of the federal poverty level—in the US Census Bureau's household pulse survey between 2021 and 2024. A difference-in-differences analysis was used to examine




**Trends in health insurance coverage and employment in Georgia and Medicaid non-expansion states**

**COMMENTARY** Plans for national rollout not supported by evidence from Georgia

On 4 July 2025, President Trump signed a budget reconciliation package that included major changes to Medicaid: all states that have adopted the Affordable Care Act's Medicaid expansion will need to implement work requirements for enrollees covered under the expansion by 1 January 2027. As the only state with an active Medicaid work requirement in 2025, Georgia's Pathways to Coverage programme is a clear antecedent for this aspect of the "Big Beautiful Bill." But what do we know about how the programme is working in Georgia?

In their study, Johnson and colleagues evaluated the impact of Georgia's Pathways to Coverage programme.[1] Pathways to Coverage is one of dozens of state Medicaid demonstration projects authorised by the Centers for Medicare and Medicaid Services (CMS) as part of the Section 1115 waiver programme. Using data from the US Census Bureau's household pulse survey, the authors compared Georgia with neighbouring non-expansion states and with a state that expanded Medicaid without work requirements. They concluded, "work requirements with Medicaid expansion in Georgia did not increase health insurance coverage or employment."

In the context of current American health policy, this article highlights a key question:

**By the time we can tell if work requirements function as intended, it may be too late**

when can we tell if a policy works? When the independent evaluators of Pathways to Coverage produced their interim report in December 2024, they ruled that a 13 month period was too short to assess the programme's impact.[2] Their caution is understandable: initial implementation of Pathways to Coverage was affected by the covid-19 pandemic, which led to CMS withdrawing approval for the demonstration project in February 2021.[3] After further discussion and litigation, the programme was implemented in July 2023.[4] These delays, along with concurrent factors like Medicaid unwinding, did not create optimal conditions for the programme's introduction.

### Lack of impact

However, Johnson and colleagues' findings suggest Georgia may be the first state to participate in Medicaid expansion without noticeably expanding Medicaid. Given how Georgia battled with CMS to expand Medicaid on its preferred terms, it is anticlimactic to learn that Georgia closely resembled neighbouring non-expansion states even after its expansion. Pathways to Coverage had no apparent impact on the rates of Medicaid coverage, uninsurance, or employment among low income Georgians between July 2023 and September 2024. Although a longer time period could reveal more, these outcomes are relatively responsive to changes in the policy environment. If none of them have moved the needle in 15 months, it may be that the needle is not going to move.

At the moment, we have no way of knowing whether Johnson and colleagues' discouraging findings represent a turbulent takeoff for Pathways to Coverage or a complete failure to launch. The programme's effectiveness falls somewhere between unsatisfactory and unknown, and many questions remain. This is to be expected for a new demonstration project that has barely completed its evaluation period. This is also why it is unusual to have a project in this stage of development serve as a template for a national level policy. Medicaid demonstration projects are like any other kind of prototype—original, interesting, and often still rough around the edges. Identifying issues and making improvements is an intended part of the process. In fact, Georgia has already received CMS approval for a modified version of Pathways to Coverage that will incorporate changes based on the interim evaluation report.[5]

### Many risks ahead

Owing to the withdrawal and eventual reinstatement of its waiver, Pathways to Coverage began implementation

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changes in Medicaid coverage, uninsured rate, and employment after Georgia implemented Medicaid expansion with work requirements (making insurance coverage conditional on working or participating in eligible activities each month) compared with neighbouring states that did not expand Medicaid, referred to as non-expansion states. To isolate the effects of work requirements, outcomes were compared between Georgia and South Dakota, a state that simultaneously underwent Medicaid expansion without work requirements.

**Study answer and limitations** After Medicaid expansion with work requirements, Medicaid coverage did not change in Georgia (35.5% to 32.4%) or in neighbouring control states (39.6% to 39.3%), resulting in no differential change between these states (difference-in-differences −3.0 percentage points, 95% confidence interval −7.6 to 1.6). These patterns were similar for the uninsured rate and employment. In a secondary analysis that aimed to isolate the effects of work requirements, Medicaid coverage decreased in Georgia compared with South Dakota (difference-in-differences −11.7 percentage points, −19.5 to −3.9), while the uninsured rate and employment did not change in these two states. Study limitations included a reliance on self-reported outcomes and a low survey response rate.

**What this study adds** Insurance coverage and employment did not increase after Georgia implemented Medicaid expansion with work requirements.

**Funding, competing interests, and data sharing** Funded by the Patrick and Catherine Weldon Donaghue Research Foundation Greater Value Portfolio Grant. No competing interests declared. Study used publicly available data.

of its Medicaid work requirement two years later than planned. A requested extension of the demonstration's end date was denied. As a result, on 30 September 2025, Georgia's Pathways to Coverage programme concluded its official and original evaluation period.[2] The programme's summative evaluation report will be submitted to CMS no later than 31 March 2027. Soon after, the public will learn if the programme achieved its goals according to the independent evaluators.

We will learn their conclusions about how Medicaid work requirements affect outcomes like employment, Medicaid enrolment, and uninsurance rates. Unfortunately, we will learn all this several months after most states have added work requirements to their Medicaid programmes as required by the "Big Beautiful Bill."

However long it takes, determining whether a policy works is a necessary step before deciding to expand its reach. Omitting this step in the case of Medicaid work requirements means exposing Medicaid enrollees to undemonstrated benefits and unknown risks. For the millions of Americans who depend on Medicaid for their health insurance coverage, by the time we can tell if work requirements function as intended, it may be too late.

**Cite this as:** *BMJ* 2025;391:r2124

Find the full version with references at http://dx.doi.org/10.1136/bmj.r2124

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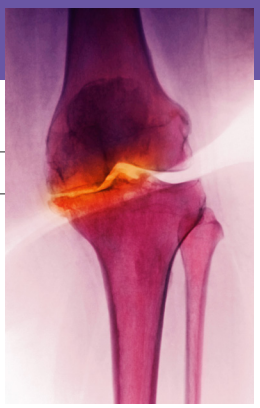


CALLISTA IMAGES/CONNECT/ALAMY

**ORIGINAL RESEARCH** Systematic review and network meta-analysis

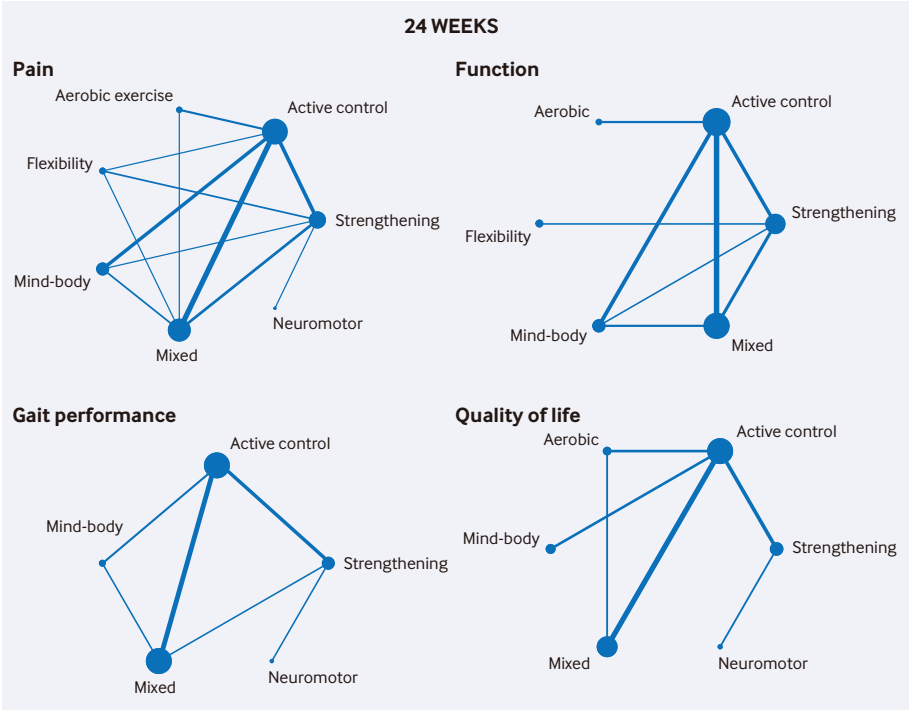
# Comparative efficacy and safety of exercise modalities in knee osteoarthritis

Yan L, Li D, Xing D, et al

**Cite this as:** *BMJ* 2025;391:e085242
Find this at doi: 10.1136/bmj-2025-085242

**Study question** Which types of exercise provide the greatest overall benefit for patients with knee osteoarthritis?

**Methods** A systematic review and network meta-analysis included 217 randomised controlled trials (with 15 684 participants in total) comparing different exercise interventions for knee osteoarthritis. Eligible trials evaluated aerobic, flexibility, strengthening, mind-body, neuromotor, and mixed exercise, in addition to control interventions. Primary outcomes were pain, physical function, gait performance, and quality of life, assessed at short term (four weeks), mid-term (12 weeks), and long term (24 weeks) follow-up.




**Network graphs of direct comparisons at 24 week follow-up. Line width is proportional to the number of studies comparing each pair of treatments, and node size is proportional to the number of participants (sample size)**

**Study answer and limitations** For patients with knee osteoarthritis, moderate certainty evidence showed that aerobic exercise is likely the most beneficial exercise modality for improving pain at short term (standardised mean difference −1.10, 95% confidence interval −1.68 to −0.52) and mid-term (−1.19, −1.59 to −0.79) follow-up. Aerobic exercise also improved function (1.78, 1.05 to 2.51) and gait performance (0.85, 0.55 to 1.14) at mid-term follow-up, as well as quality of life (1.53, 0.47 to 2.59) at short term follow-up, with moderate certainty. The study was, however, limited by most data resulting from indirect comparisons, some outcomes lacking long term data, and small study effects potentially influencing findings.

**What this study adds** Aerobic exercise may be the most beneficial exercise modality for improving pain, function, gait performance, and quality of life in patients with knee osteoarthritis.

Funding, competing interests, and data sharing
Supported by the National Natural Science Foundation of China and several Zhejiang provincial funding programmes. No competing interests declared. Data and statistical codes used for the analysis are available from the corresponding author on reasonable request.

Systematic review registration PROSPERO CRD42023469762.

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**Chen Y, et al. Anti-CD38 monoclonal antibody CM313 for primary immune thrombocytopenia: multicentre,randomised, placebo controlled, phase 2 trial. *BMJ* 2025;391:e084314. doi:10.1136/bmj-2025-084314.**

Effects of CM313 in primary immune thrombocytopenia.

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