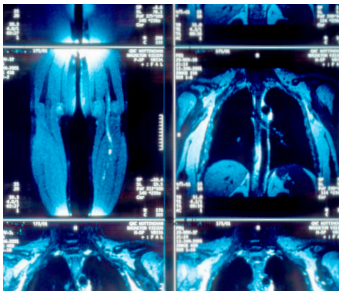
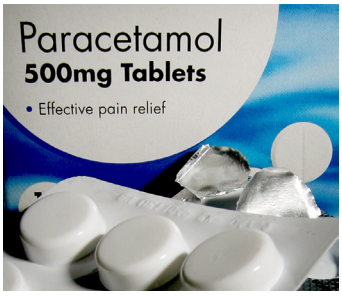
research

Impact of gestational weight gain p 189



Anticoagulation for venous thromboembolism p 192



Paracetamol use during pregnancy and risk of ASD and ADHD p 194

Adverse outcomes associated with gestational weight gain

ORIGINAL RESEARCH Systematic review and meta-analysis

Gestational weight gain and risk of adverse maternal and neonatal outcomes in observational data from 1.6 million women

Goldstein R, Bahri Khomami M, Tay CT, et al

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Study question What is the effect of gestational weight gain (GWG) outside of recommendations on adverse maternal and neonatal outcomes?

Methods This systematic review and meta-analysis included observational studies in all languages, with a population of more than 300 singleton pregnancies in women aged >18 years, from 2009 to 2024, which reported the effect of total GWG stratified by body mass index (BMI) on any maternal and neonatal outcome.

Study answer and limitations 40 studies (n=1 608 711) met the inclusion criteria; 6% (n=65 114) of women had underweight, 53% (n=607 258) had normal weight, 19% (n=215 183) had overweight, and 22% (n=252 970) had obesity. GWG was below or above Institute of Medicine or study specific recommendations in 23% and 45%, respectively. Using World Health Organization BMI criteria, GWG below Institute of Medicine recommendations was associated with lower birth weight, lower rates of caesarean delivery, large for gestational age infants, and macrosomia, and higher rates of preterm birth, small for gestational age infants, low birth weight, and respiratory distress. GWG above recommendations was associated with higher birth weight, higher rates of caesarean delivery, hypertensive disorders of pregnancy, large for gestational age infants, macrosomia, and neonatal intensive care unit admission, and lower rates of preterm birth and small for gestational age infants. Heterogeneity in BMI and GWG classifications prevented pooling for some of the studies owing to non-comparable GWG and/or BMI categorisations.

Summary of outcomes for gestational weight gain (GWG) less than or more than recommended (in studies using WHO BMI categories)

Outcome	No of studies	No of women	GWG less than recommended				GWG more than recommended			
			Odds ratio (95% CI)	I^2 (%)	P value*	Direction	Odds ratio (95% CI)	I^2 (%)	P value*	Direction
Caesarean delivery	10	122 640	0.90 (0.84 to 0.97)	38.99	0.03	Lower risk	1.37 (1.30 to 1.44)	17.82	0.08	Higher risk
Hypertensive disorders of pregnancy	6	90 965	1.00 (0.93 to 1.08)	0	0.3		1.37 (1.28 to 1.48)	40.2	0.31	Higher risk
Preterm birth	7	66 819	1.63 (1.33 to 1.90)	69.27	0	Higher risk	0.71 (0.64 to 0.79)	22.45	0.45	Lower risk
Small for gestational age	14	757 516	1.49 (1.37 to 1.61)	79.99	0	Higher risk	0.69 (0.64 to 0.75)	83.16	0	Lower risk
Low birth weight	5	11 688	1.78 (1.48 to 2.13)	0	0.37	Higher risk	0.71 (0.48 to 1.04)	42.13	0.15	
Large for gestational age	16	757 122	0.67 (0.61 to 0.74)	80.36	0	Lower risk	1.77 (1.62 to 1.94)	91.04	0	Higher risk
Macrosomia	8	78 950	0.68 (0.58 to 0.80)	17.47	0.24	Lower risk	1.78 (1.60 to 1.99)	44.6	0.02	Higher risk
Neonatal intensive care unit admission	4	19 609	0.91 (0.75 to 1.09)	0	0.46		1.26 (1.09 to 1.45)	0	0.44	Higher risk
Respiratory distress syndrome	2	1252	1.29 (1.01 to 1.63)	0	0.98	Higher risk	1.10 (0.78 to 1.56)	0	0.95	
Hyperbilirubinaemia	2	1252	0.90 (0.53 to 1.51)	0	0.76		0.93 (0.28 to 3.14)	38	0.17	

BMI=body mass index; CI=confidence interval; WHO=World Health Organization.
*P value for heterogeneity (Q test).

COMMENTARY Evidence supports a nuanced approach across the maternal life course

Gestational weight gain (GWG) remains one of the most closely monitored yet misunderstood aspects of prenatal care. For decades, healthcare systems relied on numerical targets to guide women's GWG, even with growing evidence suggesting that these thresholds may not serve all populations equally well.[1-3] The dilemma between standardisation and personalisation underscores the urgent need to move beyond pregnancy-only models of care towards prevention strategies that begin before conception and continue throughout the interpregnancy interval—the time between the end of one pregnancy and the beginning of the next.[4]

Goldstein and colleagues' systematic review reopens this debate, synthesising findings from more than 100 studies linking GWG to maternal and perinatal outcomes.[3] The authors show that both insufficient and excessive GWG are associated with increased risks, including preterm birth and small for gestational age infants at one end and macrosomia and postpartum weight retention at the other.[1-8] However, observational studies suggest that higher pre-pregnancy body mass index (BMI) has a greater impact on pregnancy complications and childhood weight than GWG, showing that many of the apparent risks of excessive GWG are attenuated once pre-pregnancy BMI is considered.[1-11] Although this underscores the considerable impact of preconception health, maintaining healthy weight, especially before but also during pregnancy, remains important to reduce obesity related risks for both mother and baby.[1-11]

Investment in integrated maternal health surveillance systems is urgently needed

A continuous relation

Although the review largely confirms longstanding knowledge, its most striking insight is the considerable variation across categories of BMI and regions, challenging the black and white logic that underpins many clinical guidelines.[2 3] Rather than a fixed weight gain threshold existing, the relation between GWG and outcomes seems to be continuous, context dependent, and shaped by preconception factors such as pre-pregnancy BMI and the wider psychosocial

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What this study adds This study assessed broad outcomes across 1.6 million pregnancies, providing an important update to previous studies by including contemporary populations across five WHO world regions and a broad BMI range. These findings directly inform the development of contextually relevant, globally applicable GWG standards for antenatal care.

Funding, competing interests, and data sharing The study was funded by the National Health and Medical Research Council of Australia, the Heart Foundation, and Veski. No competing interests declared. The original individual study data are available on reasonable request.

Study registration PROSPERO CRD42023483168.

environment.[1-12] Therefore, a more nuanced approach is urgently needed, one that recognises diversity not as noise to be adjusted for but as the basis for more integrated care.[13]

Beyond pregnancy and across the life course

Pregnancy is not an isolated episode but part of a wider health trajectory that spans the preconception, antenatal, postpartum, and interpregnancy periods. Women's preconception weight and their postpartum weight retention profoundly influence the health of both mothers and their offspring.[4-10] Moreover, high preconception or interpregnancy weight gain increases the likelihood of delivering a large for gestational age infant, who in turn faces a greater risk of obesity.[9-15] Sibling studies further show that maternal obesity at the onset of pregnancy, excessive GWG, and short interpregnancy intervals are all independently associated with overweight and obesity in offspring.[10 15] These patterns confirm that maternal and child health are deeply intertwined across the life course.

Nevertheless, preconception and interpregnancy periods, often overlooked in both research and practice, represent critical yet underutilised opportunities for intervention.[6 15] With nearly 40% of pregnancies being unplanned,[16] many women first seek antenatal care well into the first trimester, when the most sensitive developmental window has passed. Supporting healthy weight before conception and between pregnancies could therefore be more effective than focusing solely on weight management during pregnancy.[4]

Data gaps and (un)coordinated policies

Despite its centrality to maternal and child health, monitoring of weight and related outcomes remains fragmented. A recent comparison by the EuroPeristat Group showed major inconsistencies in how countries collect and link data on mothers and children.[17] Few routinely capture pre-pregnancy BMI, and most rely on self-reported measures or first visit weights. Linkages between pregnancy, birth, and child growth registries are rare, hindering the ability to track trends or evaluate interventions.

Investment in integrated maternal health surveillance systems is urgently needed. Harmonised indicators of preconception BMI, GWG, and postpartum weight retention should be incorporated into national datasets and routinely linked with child growth records. Ideally, these systems would also connect with patient reported outcome and experience measures, offering a more holistic understanding of women's health, ensuring that guidelines reflect both lived experience and epidemiological evidence.

Need for systematic change

Advising women to adhere to numerical targets overlooks the biosocial diversity that shapes pregnancy. Rather than warning all women against exceeding fixed cut-offs, clinicians may instead focus on patterns of weight gain, its underlying determinants, and personalised, non-punitive counselling.[18]

Supporting healthy GWG requires more than perinatal advice; it depends on continuity of care. Too often, healthcare engagement begins only once pregnancy is confirmed and ends soon after delivery, missing critical prevention windows. Integrating preconception counselling into routine care and ensuring extended postpartum follow-up would allow clinicians to act earlier and sustain support for longer.

At the policy level, (inter) national health authorities must move beyond narrow biomedical frameworks. Just as child growth charts are adapted to reflect biological and regional diversity, GWG recommendations should also be context specific rather than universally prescribed. This context sensitive approach calls for integrated interventions that combine weight management, nutrition counselling, and psychosocial support such as interpregnancy coaching for a healthy future,[6] the Healthy Life Trajectories Initiative,[19] and Healthy Adaptation to Pregnancy, Postpartum and Parenthood.[20] These models have the potential to not only achieve more meaningful outcomes than antenatal weight monitoring alone but also strengthen data systems, generating evidence for future policy and practice.

Maternal obesity is not merely an individual problem; it is a systemic challenge. Without comprehensive, life course strategies, the obesity epidemic will continue across generations.

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Duration of anticoagulation for unprovoked venous thromboembolism

ORIGINAL RESEARCH Emulation of a target trial

Continued versus discontinued oral anticoagulant treatment for unprovoked venous thromboembolism

Lin KJ, Kim DH, Singer DE, et al

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Study question How do the health outcomes among patients receiving extended oral anticoagulation for venous thromboembolism (VTE) compare with those who discontinue treatment?

Methods This study used two national US claims databases: Optum Clinformatics Data Mart (1 January 2009 to 28 February 2025) and Medicare fee-for-service claims (1 January 2009 to 31 December 2022). Eligible patients were aged ≥18 years who had newly initiated an oral anticoagulant (OAC, warfarin, apixaban, rivaroxaban, dabigatran, or edoxaban) within 30 days after a first time hospital admission with VTE without reversible provoking factors and continued treatment for at least 90 days. Those who continued treatment were compared with those who discontinued treatment, with discontinuation defined as an absence of a refill within 30 days after the initial 90 day treatment period. Propensity score matching was used to balance a total of 89 baseline patient characteristics. The primary outcomes were hospital admission for recurrent VTE (effectiveness) and major bleeding (safety). A secondary outcome was net clinical benefit (a composite of recurrent VTE and bleeding).

Study answer and limitations The study cohort included 30 554 propensity score matched pairs who had continued or discontinued an OAC (mean age 73.9 years, 57.0% women). After initial anticoagulation of ≥90 days, compared with those who discontinued treatment, those who continued treatment had markedly lower rates of recurrent VTE (adjusted hazard ratio 0.19, 95% confidence interval (CI) 0.13 to 0.29; adjusted rate difference per 1000 person years −25.50, 95% CI −39.38 to −11.63), higher rates of major bleeding (1.75 (1.52 to 2.02), and 4.78 (1.95 to 7.61)). The net clinical benefit, accounting for both VTE recurrence and major bleeding events, favoured OAC continuation regardless of OAC type or length of anticoagulation, even beyond 1080 days. Additionally, patients who continued treatment had a lower mortality rate compared with those who discontinued treatment (0.74 (0.69 to 0.79), and −14.31 (−22.02 to −6.59)). The results were not explained by the presence of unmeasured confounders, as expressed by the E value (a measure to assess the robustness of causality against potential confounding).[9]

COMMENTARY Patient preferences key to weighing benefits and risks of indefinite treatment

Determining the optimal duration of anticoagulation treatment after a first event of unprovoked venous thromboembolism (VTE) remains challenging.[1] Part of the difficulty lies in identifying patients who are most likely to benefit from extended anticoagulation, a treatment associated with lower VTE recurrence rates but at the cost of higher bleeding risk.[2-4] Uncertainty remains because clinical trials and prospective studies on this topic offer a limited duration of follow-up and often include highly selected participants.[5-7]

In their study, Lin and colleagues provide further real world data to help determine the risk-benefit balance of indefinite anticoagulation treatment in patients with a first, unprovoked VTE by analysing two large American databases, Optum Clinformatics Data Mart and Medicare.[8] Within these databases, adults without reversible risk factors for a first VTE were identified. Patients who continued oral anticoagulant (OAC) treatment were matched 1:1 to those who discontinued treatment using a propensity score, after having completed at least 90 days of anticoagulation. Patients who discontinued treatment were defined as those who did not refill an anticoagulation prescription within a 30 day period, at any time beyond the initial 90 day anticoagulation treatment phase for a first VTE event. Matching was done based on duration from the index VTE and type of index VTE (pulmonary embolism or deep vein thrombosis), as well as 89 relevant baseline characteristics. Through this method, the authors identified 30 554 propensity score matched pairs. Compared with patients who discontinued OAC treatment, patients who continued treatment had lower rates of VTE recurrence (adjusted hazard ratio 0.19 (95% confidence interval (CI) 0.13 to 0.29), and adjusted risk difference per 1000 person years −25.50 (95% CI −39.38 to −11.63)), but higher rates of major bleeding (1.75 (1.52 to 2.02), and 4.78 (1.95 to 7.61)). The net clinical benefit, accounting for both VTE recurrence and major bleeding events, favoured OAC continuation regardless of OAC type or length of anticoagulation, even beyond 1080 days. Additionally, patients who continued treatment had a lower mortality rate compared with those who discontinued

The net clinical benefit persists when OACs are continued even beyond three years

Important follow-up data

This study adds to the literature on this topic by using a target trial emulation analysis with a large sample size of more than 60 000 patients. More importantly, it provides long term follow-up data, which show that the net clinical benefit persists when OACs are continued even beyond three years. However, despite the extensive propensity matching, limitations remain unavoidable when using such retrospective databases, which the authors acknowledge. Residual confounding may still be present and could contribute to the mortality benefit seen in patients who continued OAC treatment. Furthermore, the risk-benefit calculations provided here do not necessarily translate to improved quality of life, respect of patient values and preferences, or cost-benefit to the healthcare system. Such perspectives are beyond the scope of this study but can be important for further investigation.

What clinical implications can be derived from this current paper? It is generally

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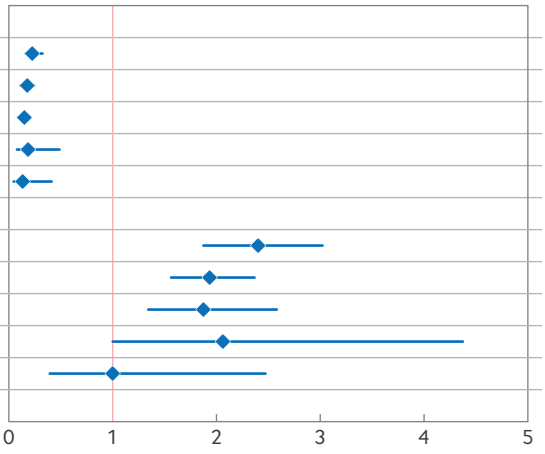
bleeding (1.75, 1.52 to 2.02; 4.78, 1.95 to 7.61), and greater net clinical benefit (0.39, 0.36 to 0.42; −21.01, −32.31 to −9.71). Residual confounding cannot be ruled out as the data lacked information on over-the-counter drug use, socioeconomic status, laboratory test results, and reasons for discontinuing oral anticoagulation.

What this study adds Based on two US national claims databases, patients with unprovoked VTE who continued OAC treatment after initial anticoagulation for at least 90 days experienced substantially lower rates of VTE recurrence and higher rates of major bleeding compared with patients who discontinued treatment.

Length of initial treatment (days)	Adjusted hazard ratio (95% CI)
Recurrent VTE	
90-179	0.22 (0.16 to 0.32)
180-359	0.17 (0.13 to 0.23)
360-719	0.15 (0.11 to 0.20)
720-1079	0.18 (0.07 to 0.49)
≥1080	0.13 (0.04 to 0.41)
Major bleeding	
90-179	2.38 (1.88 to 3.02)
180-359	1.92 (1.56 to 2.37)
360-719	1.85 (1.34 to 2.57)
720-1079	2.04 (0.96 to 4.36)
≥1080	1.00 (0.40 to 2.48)



Subgroup analysis comparing patients who continued versus discontinued an oral anticoagulant by number of days after initial treatment. VTE=venous thromboembolism

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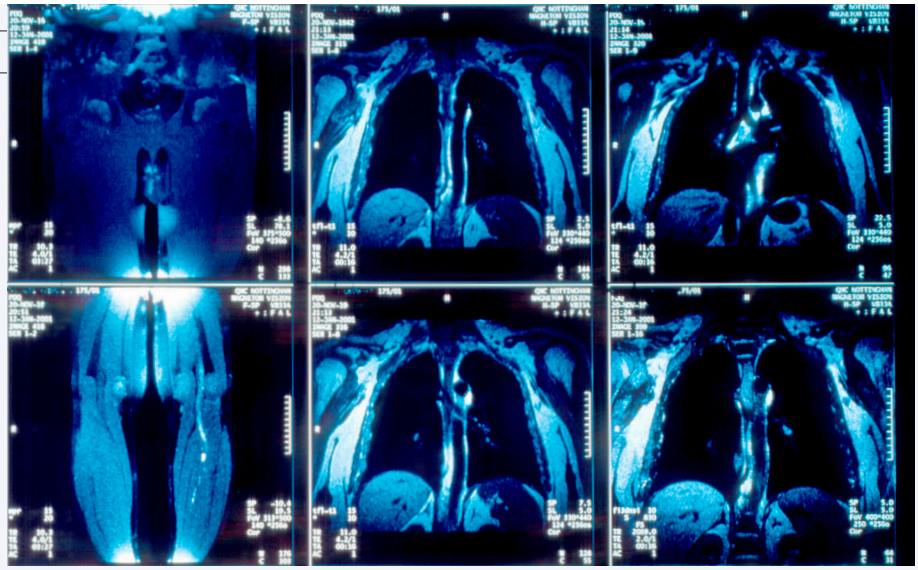

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accepted that major bleeding events in patients receiving extended anticoagulation confer a 2-3 times higher mortality risk than recurrent VTE.[10-12] As such, one would expect continuation of OACs to confer a VTE risk difference to be at least 2-3 times larger than the risk difference of increased major bleeding events, to make this intervention worthwhile from a mortality perspective. When balancing the risks and benefits of continued anticoagulation, clinicians can provide patients with such a framework to help guide decision making on treatment duration. The results from this study are consistent with previous studies on this topic and do support the use of continued oral anticoagulation based on the point estimate of risk difference, although some uncertainty remains when considering the full width of the 95% CI. The risk differences described here might be useful to clinicians when counselling patients on the expected risks and benefits of continued oral anticoagulation treatment. Engaging with patients, however, remains necessary to account for personal preferences and values about the duration of treatment in view of this persistent uncertainty.

Prioritising DOACs

Furthermore, the choice of anticoagulant could matter. This study showed that among those who continued OAC treatment, direct oral anticoagulants (DOACs) seemed safer compared with warfarin. Additional areas of clinical equipoise to consider, not covered here, include the impact of DOAC dose reduction in the extended phase, which could further reduce the bleeding risks. Recently, the RENOVE trial showed that after at least six months of initial anticoagulation, continuing either full or reduced dose DOAC was associated with a low rate of recurrent VTE (five year cumulative incidence 1.8-2.2%), with the reduced dose regimen resulting in fewer clinically relevant bleeding events compared with full dose (five year cumulative incidence 9.9% *v* 15.2%, hazard ratio 0.61 (95% CI 0.48 to 0.79).)[13] Additionally, use of biomarkers such as D-dimer, if available, could be helpful in the risk stratification for recurrent VTE.[14 15]

In summary, Lin and colleagues' study provides clinicians and patients with good insight on the effectiveness and safety of long term OAC treatment, by leveraging large, real world databases to summarise the net clinical benefit associated with this intervention.

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Maternal paracetamol use during pregnancy and risk of autism spectrum disorder and attention deficit/hyperactivity disorder in offspring

Sheikh J, Allotey J, Sobhy S, et al

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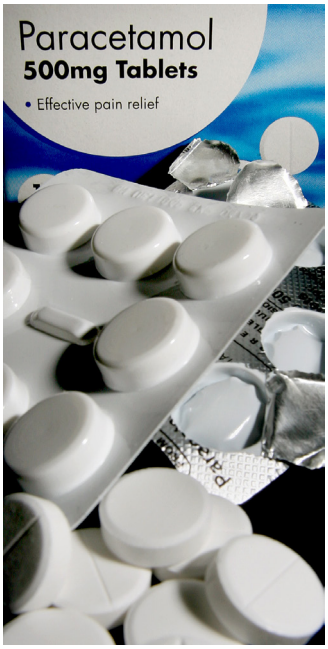

PA/ALAMY

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Paracetamol is the recommended treatment for pain and fever in pregnancy and is considered safe by regulatory agencies worldwide
- Systematic reviews and primary studies vary in their reporting on maternal paracetamol use during pregnancy and risk of autism spectrum disorder (autism) and attention deficit/hyperactivity disorder (ADHD) in offspring

WHAT THIS STUDY ADDS

- Confidence in the findings of published systematic reviews on maternal paracetamol use during pregnancy and risk of autism and ADHD in offspring, with a very high overlap of primary studies, is low to critically low
- Existing evidence does not show a clear link between in utero exposure to paracetamol and autism and ADHD in offspring
- Any apparent effect observed after in utero exposure to paracetamol on autism and ADHD in childhood might be driven by familial genetic and environmental factors and unmeasured confounders

Study question What is the evidence for maternal paracetamol use during pregnancy and risk of autism spectrum disorder (referred to as autism) and attention deficit/hyperactivity disorder (ADHD) in offspring?

Methods Medline, Embase, PsycINFO, the Cochrane Database of Systematic Reviews, Epistemonikos, grey literature, and reference lists were searched from inception to 30 September 2025 for systematic reviews on in utero exposure to paracetamol and autism or ADHD in children. The AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) tool was used to assess review quality. The review findings are reported along with details of the included primary studies, any adjustments for key confounders (maternal characteristics, indication for paracetamol use, and familial factors) and unmeasured confounders, and outcome ascertainment.

Study answer and limitations Nine reviews (40 studies) reporting on autism (six studies) and ADHD (17 studies) in offspring were included. The overlap of primary studies in the reviews was very high (corrected covered area 23%). Possible to strong associations were reported between maternal paracetamol use and autism or ADHD in offspring. Seven reviews advised caution in interpreting the findings owing to potential bias and confounding in the included studies. Confidence in the review findings was low (two reviews) to critically low (seven reviews). Only one review included studies (n=2) that appropriately adjusted for familial factors and unmeasured confounding through sibling controlled analysis. The observed association in whole cohort analyses between maternal paracetamol use and autism or ADHD in offspring did not persist in sibling controlled analyses. One limitation was that the effects on other neurodevelopmental outcomes were not assessed.

What this study adds Existing evidence does not clearly link maternal paracetamol use during pregnancy with autism or ADHD in offspring. Any apparent effect might have been driven by familial genetic and environmental factors and unmeasured confounders.

Funding, competing interests, and data sharing Author ST is a senior investigator for the National Institute for Health and Care Research (NIHR). SS is funded by the NIHR Midlands Patient Safety Research Collaboration. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. The Instituto de Salud Carlos III supports HMB through a Río Hortega contract (CM24/00152), co-funded by European Social Fund Plus. No competing interests declared. Data extracted from published sources are included in the article and supplementary material.

Systematic review registration PROSPERO CRD420251154052.

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