research

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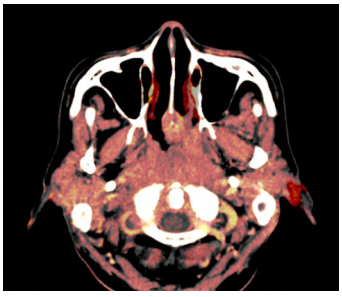

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Preventing postoperative delirium

ORIGINAL RESEARCH Systematic review and network meta-analysis of randomised controlled trials

Effectiveness of drug interventions to prevent delirium after surgery for older adults

Luney M, Holdsworth L, Hanaga A, et al

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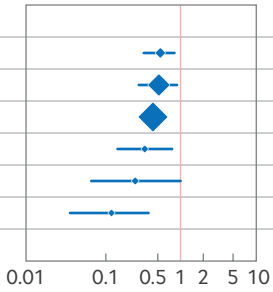
Study question Which drugs are effective at preventing delirium after surgery in older adults?

Methods This systematic review and bayesian arm based network meta-analysis evaluated drugs to prevent postoperative delirium. Randomised controlled trials were eligible for inclusion if they enrolled participants aged ≥60 years and assessed delirium with a validated tool. Studies of surgery done under local anaesthesia, those with preoperative mechanical ventilation, and delirium treatment studies were excluded. Embase, Medline, and the Cochrane Library were searched up to 4 March 2024. Screening, data extraction, and assessments of risk of bias and evidence quality were independently completed in duplicate. The primary outcome was incidence of postoperative delirium; secondary outcomes were delirium severity, length of stay, mortality, cognition, quality of life, and adverse events.

Study answer and limitations Across 158 trials including 41 084 participants and 52 interventions, the overall risk of delirium after surgery was 14.5% (n=5957). Dexmedetomidine (odds ratio 0.46, 95% credible interval 0.36 to 0.57), corticosteroids (0.53, 0.31 to 0.87), melatonin receptor agonists (0.54, 0.34 to 0.85), parecoxib (0.34, 0.16 to 0.74), olanzapine (0.27, 0.07 to 0.94), and intranasal insulin (0.13, 0.04 to 0.34) were associated with lower delirium incidence in trials not at high risk of bias. Quality of evidence ranged from moderate to very low. Limitations included trials at high risk of bias and inconsistencies in outcome reporting.

Intervention	No of participants	No of trials	Odds ratio (95% CrI)
Melatonin receptor agonists	759	12	0.54 (0.34 to 0.85)
Corticosteroids	4460	8	0.53 (0.31 to 0.87)
Dexmedetomidine	7156	66	0.46 (0.36 to 0.57)
Parecoxib	425	4	0.34 (0.16 to 0.74)
Olanzapine	243	1	0.27 (0.07 to 0.94)
Insulin (intranasal)	105	3	0.13 (0.04 to 0.36)

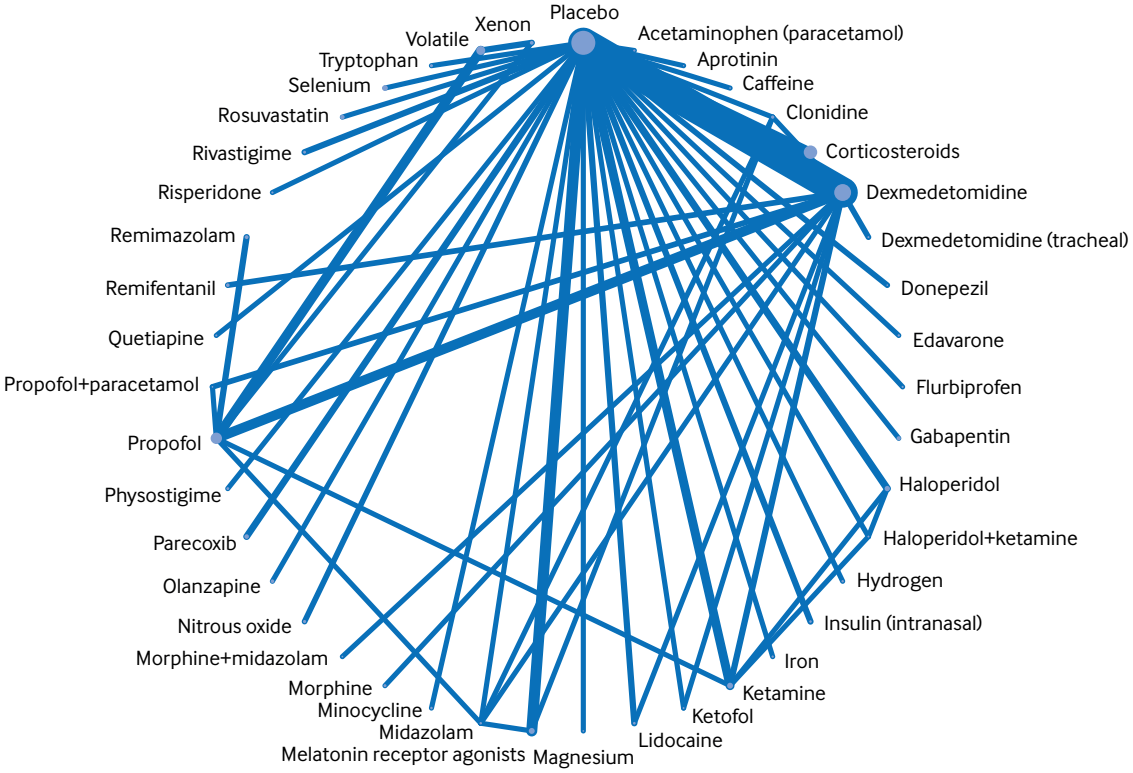


Forest plot of network meta-analysis results for randomised controlled trials of drugs to prevent delirium after surgery, excluding trials at high risk of bias. Reference intervention is placebo. Box sizes correspond to number of participants. CrI=credible interval

What this study adds Moderate certainty evidence shows that dexmedetomidine is effective at preventing delirium across surgical specialties. Corticosteroids, melatonin receptor agonists, insulin, parecoxib, and olanzapine are potentially effective, but more studies are needed to overcome low quality evidence from trials at high risk of bias and small study effects.

Funding, competing interests, and data sharing
Funded by the National Institute for Health and Care Research (NIHR) Doctoral Research Fellowship and the NIHR Oxford Biomedical Research Centre. See full paper on bmj.com for competing interests. No additional data available.

Study registration PROSPERO CRD42023488337.



Network graph of randomised controlled trials of drug prophylaxis against postoperative delirium depicting connectedness of networks excluding trials at high risk of bias. Node sizes correspond to number of participants in comparison arm; thickness of edges correspond to number of studies within that pair of direct comparisons

COMMENTARY Multi-component interventions likely to be most effective but need further evaluation

Postoperative delirium is an acute disturbance in attention, awareness, and cognition, often involving hallucinations, disorganised thinking, and severe confusion that occurs in the week after surgery.[1] It is highly distressing for patients and families, is challenging for staff to manage, and prolongs hospital stay and increases healthcare costs. It is linked to faster long term cognitive decline,[2 3] although the causal pathway remains uncertain. Reported incidence varies widely (3-30%).[4-6] Variation in assessment tools, skill of assessor, and assessment frequency can influence estimates of incidence. However, underlying brain vulnerability and the severity of surgical insult can also produce strikingly different rates in different populations. This variability means that interventions to prevent delirium must show either a modest but reliable benefit within a specific surgical context or a clear and substantial benefit across multiple settings to justify widespread clinical adoption.

In their paper, Luney and colleagues present a systematic review and network meta-analysis of drug interventions to prevent delirium after surgery.[11] They included randomised controlled trials of prescription-only drugs administered on the day of surgery to patients older than 60 years undergoing any surgical procedure (under general or regional anaesthetic), yielding 158 studies of 52 different interventions in more than 41 000 participants.

Uncertain effects

Dexmedetomidine, an α2-adrenoceptor agonist, was the only agent that showed a consistent signal of benefit, reducing the overall odds of postoperative delirium by 55%. This effect was observed across cardiac and non-cardiac (excluding thoracic) surgeries and elective and emergency surgeries, and it persisted even after exclusion of small studies and those at high risk of bias. Importantly, the benefit seemed to be independent of whether patients received general or regional anaesthesia, suggesting that it is not solely a result of sparing of propofol or volatile agents. However, the GRADE quality of evidence was low, meaning that we cannot be certain that this effect is real. Overall, the current evidence is insufficient to recommend routine changes in clinical practice.

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Non-drug interventions are the mainstay of delirium prevention

Several interventions showed potential benefits across different surgical groups. These included corticosteroids, melatonin receptor agonists, parecoxib, olanzapine, and intranasal insulin, with estimated reductions in the odds of delirium of 52-88%. However, these large effect sizes from the network meta-analysis should be interpreted with caution, as again the GRADE certainty of evidence was mostly low. Additionally, small trials or trials with heterogeneous populations, interventions, or outcome definitions may produce larger, unstable effects that may not be replicated in larger, high quality trials.

An important consideration in this review is that most interventions had no effect on length of stay, mortality, long term cognition, or quality of life. This is important and highlights that prevention alone may not translate into meaningful benefits to the patient or health system, emphasising the need for trials powered to assess both delirium and other clinically important outcomes.

Complications for clinical practice

Any intervention that is effective at preventing delirium is likely to be complex and multi-component,[12] and it would potentially comprise both drug and non-drug interventions. Non-drug interventions are the mainstay of delirium prevention.[12 13] They have a low risk of harm and are inexpensive, but they are difficult to operationalise and prescribe compared with drug interventions. This makes non-drug interventions more challenging to implement in clinical practice. They are also more difficult to combine in a meta-analysis than drug interventions because their delivery can vary widely.[14]

Luney and colleagues' review does not alter current expert consensus recommendations for preventing postoperative delirium.[13] The priority remains to identify individuals at high risk preoperatively wherever feasible and to implement a comprehensive delirium prevention bundle.[12 13] Recommended non-drug measures include promptly returning sensory aids after surgery (glasses, dentures, hearing aids); protecting sleep-wake cycles by implementation of quiet hours, low light environments at night, and the use of eye masks or earplugs; and encouraging the involvement of family or care givers, who can support measures such as reorientation. Pain should be managed proactively and effectively. Benzodiazepines should be avoided entirely and antipsychotics reserved only for patients who are acutely agitated and pose a risk to themselves or others.

Dexmedetomidine may have a role in selected patients or settings, but emerging evidence from intensive care suggests that when evaluated in adequately powered, well controlled trials with systematic adverse event reporting, dexmedetomidine may not be as benign as initially assumed, with notable increases in bradycardia and agitation.[15] Adverse event reporting in the trials included in this network meta-analysis was sparse, so we do not know enough about the harms of the drugs to make recommendations for widespread use.

To make a comprehensive delirium prevention bundle truly effective, all delirium prevention components should be embedded within a behavioural framework. This would enhance feasibility for clinical teams and acceptability for patients and families. Such complex interventions then need to be evaluated in randomised controlled trials to determine whether they improve outcomes that matter to patients (for example, quality of life) and to healthcare providers (for example, length of stay and costs). These are more likely to yield useful effects than more trials of existing drugs.

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Menopausal hormone therapy and long term mortality

Mikkelsen AP, Bergholt T, Lidegaard Ø, Scheller NM

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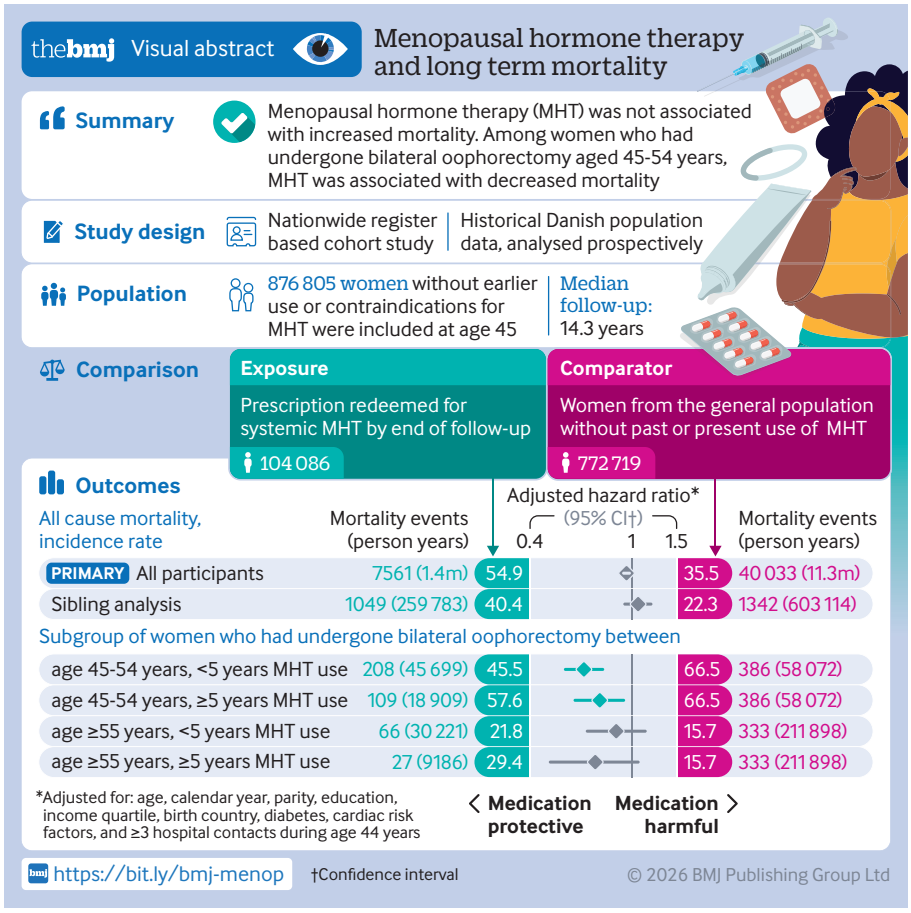
Study question Does menopausal hormone therapy increase mortality?

Methods In this Danish registry based cohort study, all women born between 1950 and 1977 and alive at age 45 years were eligible for inclusion. Follow-up for each participant began on their 45th birthday and ended on 31 July 2023. Of 969 424 eligible women, 92 619 were excluded because of thrombophilia, liver disease, arterial or venous thrombosis, breast cancer, endometrial cancer, or ovarian cancer, earlier use of menopausal hormone therapy, or earlier bilateral oophorectomy. Systemic menopausal hormone therapy was the intervention of interest. The main outcome was death as registered in the central persons register. Secondary outcomes were cause specific mortality registered in the cause of death register categorised as mortality from cardiovascular causes, cancer, or other causes. Hazard ratios were estimated using Cox regression, adjusted for age, calendar year, parity, educational qualification, income quarter, country of birth, diabetes, hypercholesterolaemia, hypertension, atrial fibrillation, valvular disease, heart failure, and three or more hospital contacts between 44 and 45 years of age.

Study answer and limitations Menopausal hormone therapy was not associated with increased mortality. Of 876 805 women, 104 086 (11.9%) redeemed a prescription for menopausal hormone therapy, and 47 594 (5.4%) died, with a median follow-up time of 14.3 years (interquartile range 7.9-21.0 years). A limitation of the study is that menopausal hormone therapy was not prescribed at random (which is possible in a controlled setting), and the study did not have data on body mass index or smoking for the entire cohort. A sibling analysis was used to investigate unmeasured confounding, which substantiated the main result.

What this study adds This study found that menopausal hormone therapy was not associated with increased mortality. Women who underwent bilateral oophorectomy between the ages of 45 and 54 years and used menopausal hormone therapy had a 27-34% lower mortality than women who did not.



GARO/PHANIE/SIPA/ALAMY

Funding, competing interests, and data sharing
Funded by a public grant from Herlev Hospital. No competing interests declared. ØL declared a grant from Exeltis outside the presented work. Data used in the current study are not openly available.

Association between menopausal hormone therapy and all cause mortality

Years of MHT use	No of mortality events	No of person years	Incidence rate*	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)†
Primary analysis					
Never used	40 033	11 285 883	35.5	1	1
Past or present use	7561	1 377 023	54.9	1.04 (1.01 to 1.06)	0.96 (0.93 to 0.98)
Primary analysis stratified by duration of use					
0 years	40 033	11 285 883	35.5	1	1
<1 year	3107	569 091	54.6	1.12 (1.08 to 1.16)	1.01 (0.98 to 1.05)
1-2.9 years	1804	369 244	48.9	0.98 (0.93 to 1.03)	0.94 (0.89 to 0.98)
3-4.9 years	979	190 191	51.5	0.94 (0.88 to 1.00)	0.90 (0.84 to 0.95)
5-9.9 years	1120	186 955	59.9	0.98 (0.92 to 1.04)	0.89 (0.84 to 0.95)
≥10 years	551	61 542	89.5	1.12 (1.03 to 1.22)	0.98 (0.90 to 1.07)
Sensitivity analysis: censored at MHT contraindication‡					
Never used	25 197	10 698 290	23.6	1	1
Past or present use	4519	1 258 033	35.9	1.04 (1.01 to 1.08)	0.97 (0.93 to 1.00)
Sensitivity analysis: sibling analysis					
Never used	1342	603 114	22.3	1	1
Past or present use	1049	259 783	40.4	1.15 (1.05 to 1.25)	1.06 (0.94 to 1.19)
Sensitivity analysis: as treated analysis (censored at MHT cessation)					
Never used	40 033	11 285 883	35.5	1	1
Past or present use	618	239 921	25.8	0.87 (0.80 to 0.94)	0.83 (0.76 to 0.89)
Subgroup of women who had undergone hysterectomy§					
0 years	2915	835 825	34.9	1	1
<5 years	907	195 203	46.5	1.08 (1.00 to 1.17)	1.02 (0.94 to 1.10)
≥5 years	339	59 683	56.8	1.02 (0.91 to 1.14)	0.94 (0.84 to 1.05)
Subgroup of women who had undergone bilateral oophorectomy at age 45-54 years§					
0 years	386	58 072	66.5	1	1
<5 years	208	45 699	45.5	0.65 (0.55 to 0.77)	0.66 (0.56 to 0.79)
≥5 years	109	18 909	57.6	0.75 (0.60 to 0.93)	0.73 (0.58 to 0.91)
Subgroup of women who had undergone bilateral oophorectomy at age 55 years or older§					
0 years	333	211 898	15.7	1	1
<5 years	66	30 221	21.8	0.87 (0.67 to 1.13)	0.88 (0.67 to 1.15)
≥5 years	27	9186	29.4	0.72 (0.48 to 1.06)	0.72 (0.48 to 1.07)
Stratified analysis: by treatment form most used					
Never used	40 033	11 285 883	35.5	1	1
Oral	6457	1 119 600	57.7	1.08 (1.05 to 1.11)	0.98 (0.95 to 1.01)
Transdermal	1098	256 122	42.9	0.85 (0.80 to 0.90)	0.85 (0.80 to 0.90)
Other formulation	6	1302	46.1	0.81 (0.36 to 1.79)	0.68 (0.30 to 1.50)
Stratified analysis: by progestogen regimen used predominantly					
Never used	40 033	11 285 883	35.5	1	1
Oestrogen monotherapy	2034	392 901	51.8	1.02 (0.97 to 1.06)	0.92 (0.88 to 0.97)
Oestrogen+cyclic progestogen	3315	597 528	55.5	1.06 (1.02 to 1.09)	0.96 (0.92 to 0.99)
Oestrogen+continuous progestogen	2212	386 594	57.2	1.03 (0.99 to 1.07)	0.99 (0.95 to 1.04)
Stratified analysis: by age of initiation					
Never use	40 033	11 285 883	35.5	1	1
45-51 years	6504	1 106 853	58.8	1.14 (1.11 to 1.18)	1.02 (1.00 to 1.05)
52-56 years	933	244 818	38.1	0.65 (0.61 to 0.70)	0.69 (0.65 to 0.74)
≥57 years	124	25 352	48.9	0.66 (0.55 to 0.78)	0.69 (0.58 to 0.83)

CI=confidence interval; MHT=menopausal hormone therapy.
*Incidence rate per 10 000 person years.
†Adjusted for age, calendar year, parity, educational degree, income quarter, country of birth, diabetes, hypercholesterolaemia, hypertension, atrial fibrillation, valvular disease, heart failure, and three or more hospital contacts during age 44 years.
‡MHT contraindications: thrombophilia, liver disease, arterial or venous thrombosis, breast cancer, endometrial cancer, or ovarian cancer.
§Censored at breast cancer, endometrial cancer, or ovarian cancer.

ORIGINAL RESEARCH Multicentre, randomised, open label, phase 3 trial

Standard chemoradiotherapy with concurrent and adjuvant camrelizumab in patients with high risk nasopharyngeal carcinoma

You R, Xu G-Q, Ding X, et al

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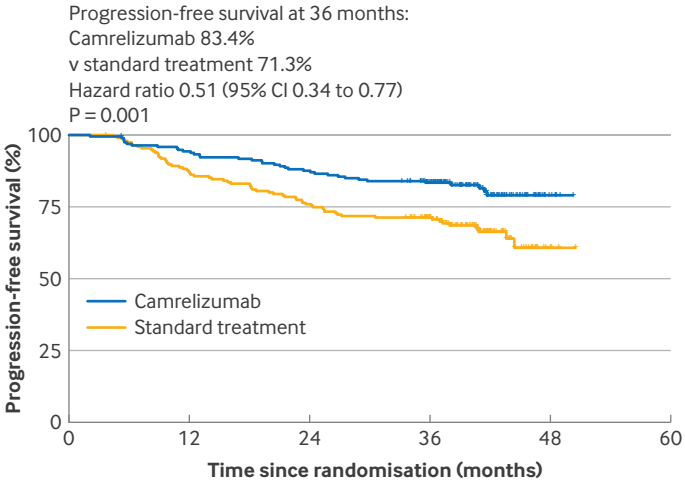
Study question Does chemoradiotherapy plus camrelizumab improve progression-free survival compared with chemoradiotherapy alone in patients with high risk nasopharyngeal carcinoma?

Methods This phase 3 trial was conducted in seven hospitals in China between 18 August 2020 and 21 June 2022. Eligible patients were aged 18-70 years with newly diagnosed high risk nasopharyngeal carcinoma and were enrolled after three cycles of induction chemotherapy with gemcitabine and cisplatin. Patients were stratified by disease stage (2-3 *v* 4a) and treatment centre and were randomly assigned (1:1) to receive cisplatin based concurrent chemoradiotherapy (standard treatment group) or standard treatment plus concurrent and adjuvant camrelizumab (camrelizumab group). The primary endpoint was progression-free survival, defined as the time from randomisation to disease recurrence (locoregional or distant) or death from any cause in the intention-to-treat population.

Study answer and limitations 390 patients were enrolled and randomly assigned to the camrelizumab group (n=194) or the standard treatment group (n=196). At median follow-up of 39.9 months (interquartile range 36.8-43.4 months), progression-free survival was higher in the camrelizumab group than the standard treatment group (36 months: 83.4%, 95% confidence interval (CI) 78.3% to 88.8% *v* 71.3%, 65.2% to 77.9%; stratified hazard ratio 0.51, 95% CI 0.34 to 0.77, P=0.001). Patients were enrolled from a region where nasopharyngeal carcinoma is predominantly linked to Epstein-Barr virus infection, therefore the generalisability of the findings to other populations needs further validation.



No at risk (No censored)					
Standard treatment	196 (1)	170 (0)	148 (21)	119 (107)	4 (4)
Camrelizumab	194 (1)	182 (0)	169 (18)	144 (132)	7 (7)

Kaplan-Meier survival analysis of intention-to-treat population at 36 months. CI=confidence interval

What this study adds The addition of camrelizumab to concurrent chemoradiotherapy and as maintenance treatment improved progression-free survival among patients with high risk nasopharyngeal carcinoma after induction chemotherapy.

Funding, competing interests, and data sharing Funding provided by Noncommunicable Chronic Diseases-National Science and Technology Major Project, National Natural Science Foundation of China, International Cooperation and Exchange of the National Natural Science Foundation of China, Jiangxi Provincial Natural Science Foundation of China. No competing interests declared. Data available at: https://doi.org/10.5061/dryad.3j9kd51zg

Trial registration ClinicalTrials.gov NCT04453826.

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Non-prospective registration in ICMJE accepted registries
You R, et al. Analysis of non-prospective trial registration in clinical trials submitted to *The BMJ*: observational study
BMJ 2025;391:e086467. http://dx.doi.org/10.1136/bmj-2025-086467