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Menopausal hormone therapy and dementia: nationwide, nested case-control study

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ABSTRACT

OBJECTIVES

To assess the association between use of menopausal hormone therapy and development of dementia according to type of hormone treatment, duration of use, and age at usage.

DESIGN

Nationwide, nested case-control study.

SETTING

Denmark through national registries.

PARTICIPANTS

treatment at the age 55 years or younger (1.24 (1.11 to 1.40)). Findings persisted when restricted to late onset dementia (1.21 (1.12 to 1.30)) and Alzheimer's disease (1.22 (1.07 to 1.39)).

CONCLUSIONS

Menopausal hormone therapy was positively associated with development of all cause dementia and Alzheimer's disease, even in women who received treatment at the age of 55 years or younger. The increased rate of dementia was similar between continuous and cyclic treatment. Further studies

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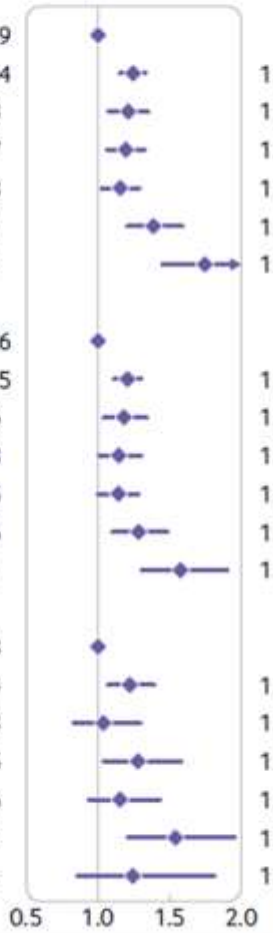
Table 2 | Use of combined menopausal hormone therapy in cases and controls

	Cases of all cause dementia (n=5589)	Controls (n=55 890)	P value
Ever users of oestrogen-progestin	1782 (31.9)	16 154 (28.9)	
Age at initiation of use, years:			
Median (interquartile range)	53 (50-54)	53 (50-54)	
45-49	331 (18.6)	2714 (16.8)	0.31
50-54	1084 (60.8)	10 051 (62.2)	
55-59	354 (19.9)	3271 (20.2)	
≥60	13 (0.7)	118 (0.7)	
Duration of use, years:			
≤1	447 (25.1)	4043 (25.0)	<0.001
>1-4	460 (25.8)	4397 (27.2)	
>4-8	447 (25.1)	4468 (27.7)	
>8-12	282 (15.8)	2311 (14.3)	
>12	146 (8.2)	935 (5.8)	
Method of treatment:			
Continuous progestin	458 (25.7)	3919 (24.3)	0.49
Cyclic progestin	694 (38.9)	6284 (38.9)	
Continuous and cyclic oestrogen and progestin	542 (30.4)	5096 (31.5)	
Unknown	88 (4.9)	855 (5.3)	
Route of administration:			
Oral administration only	1609 (90.3)	14 391 (89.1)	0.07
Transdermal administration only	56 (3.1)	462 (2.9)	
Mixed or other administration	117 (6.6)	1301 (8.1)	
Active ingredients:			
Oestradiol+norethisterone	1488 (83.5)	13 024 (80.6)	0.004
Oestradiol+medroxyprogesterone	525 (29.5)	5134 (31.8)	0.05
Oestradiol+levonorgestrel	137 (7.7)	1557 (9.6)	0.009
Oestradiol+cyproterone	77 (4.3)	874 (5.4)	0.06
Oestradiol+dienogest	40 (2.2)	270 (1.7)	0.10

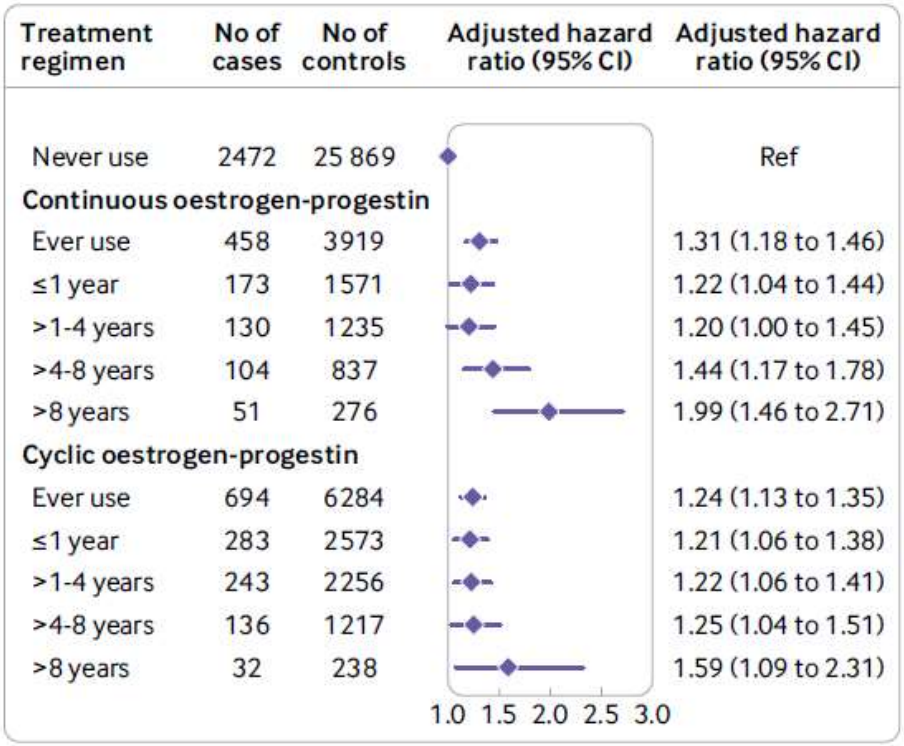
Column percentages are no of ever users of oestrogen-progestin.

BMJ 2023 Menopausal hormone therapy and dementia 2.

Oestrogen-progestin use	No of cases	No of controls	Adjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
All cause dementia				
Never use	2472	25 869		Ref
Ever use	1782	16 154		1.24 (1.17 to 1.33)
≤1 year	447	4043		1.21 (1.09 to 1.35)
>1-4 years	460	4397		1.19 (1.07 to 1.33)
>4-8 years	447	4468		1.15 (1.03 to 1.28)
>8-12 years	282	2311		1.39 (1.21 to 1.58)
>12 years	146	935		1.74 (1.45 to 2.10)
Late onset dementia				
Never use	1888	19 586		Ref
Ever use	1403	12 775		1.21 (1.12 to 1.30)
≤1 year	334	3026		1.18 (1.04 to 1.33)
>1-4 years	342	3318		1.14 (1.01 to 1.29)
>4-8 years	348	3415		1.14 (1.01 to 1.28)
>8-12 years	237	2036		1.28 (1.10 to 1.48)
>12 years	142	980		1.58 (1.31 to 1.90)
Alzheimer's disease				
Never use	623	6498		Ref
Ever use	476	4254		1.22 (1.07 to 1.39)
≤1 year	107	1083		1.04 (0.83 to 1.29)
>1-4 years	126	1105		1.28 (1.04 to 1.57)
>4-8 years	117	1136		1.15 (0.93 to 1.43)
>8-12 years	93	655		1.54 (1.21 to 1.95)
>12 years	33	275		1.24 (0.85 to 1.81)



BMJ 2023 Menopausal hormone therapy and dementia 3.



Treatment regimen	No of cases	No of controls	Adjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Never use	2472	25 869		Ref
Continuous oestrogen-progestin				
Ever use	458	3919		1.31 (1.18 to 1.46)
≤1 year	173	1571		1.22 (1.04 to 1.44)
>1-4 years	130	1235		1.20 (1.00 to 1.45)
>4-8 years	104	837		1.44 (1.17 to 1.78)
>8 years	51	276		1.99 (1.46 to 2.71)
Cyclic oestrogen-progestin				
Ever use	694	6284		1.24 (1.13 to 1.35)
≤1 year	283	2573		1.21 (1.06 to 1.38)
>1-4 years	243	2256		1.22 (1.06 to 1.41)
>4-8 years	136	1217		1.25 (1.04 to 1.51)
>8 years	32	238		1.59 (1.09 to 2.31)

BMJ 2023 Menopausal hormone therapy and dementia 4.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Large scale observational studies found long term use of menopausal hormone therapy is associated with development of dementia, confirming findings from the largest randomised, double blind, placebo controlled trial on the topic

The effect of short term use of menopausal hormone therapy around the age of menopause remains to be fully explored

Information is scarce on the effect of continuous versus cyclic combined menopausal hormone therapy on the risk of dementia

WHAT THIS STUDY ADDS

Exposure to menopausal hormone therapy was positively associated with development of all cause dementia and Alzheimer's disease, even for short term usage around the age of menopause onset

Continuous and cyclic oestrogen-progestin regimens were associated with a comparable increased rate of dementia

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human reproduction

META-ANALYSIS *Early pregnancy*

The risk of miscarriage following COVID-19 vaccination: a systematic review and meta-analysis

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The risk of miscarriage following COVID-19 vaccination 1.

Submitted on July 25, 2022; resubmitted on February 9, 2023; editorial decision on February 13, 2023

STUDY QUESTION: What is the risk of miscarriage among pregnant women who received any of the COVID-19 vaccines?

SUMMARY ANSWER: There is no evidence that COVID-19 vaccines are associated with an increased risk of miscarriage.

WHAT IS KNOWN ALREADY: In response to the COVID-19 pandemic, the mass roll-out of vaccines helped to boost herd immunity and reduced hospital admissions, morbidity, and mortality. Still, many were concerned about the safety of vaccines for pregnancy, which may have limited their uptake among pregnant women and those planning a pregnancy.

STUDY DESIGN, SIZE, DURATION: For this systematic review and meta-analysis, we searched MEDLINE, EMBASE, and Cochrane CENTRAL from inception until June 2022 using a combination of keywords and MeSH terms.

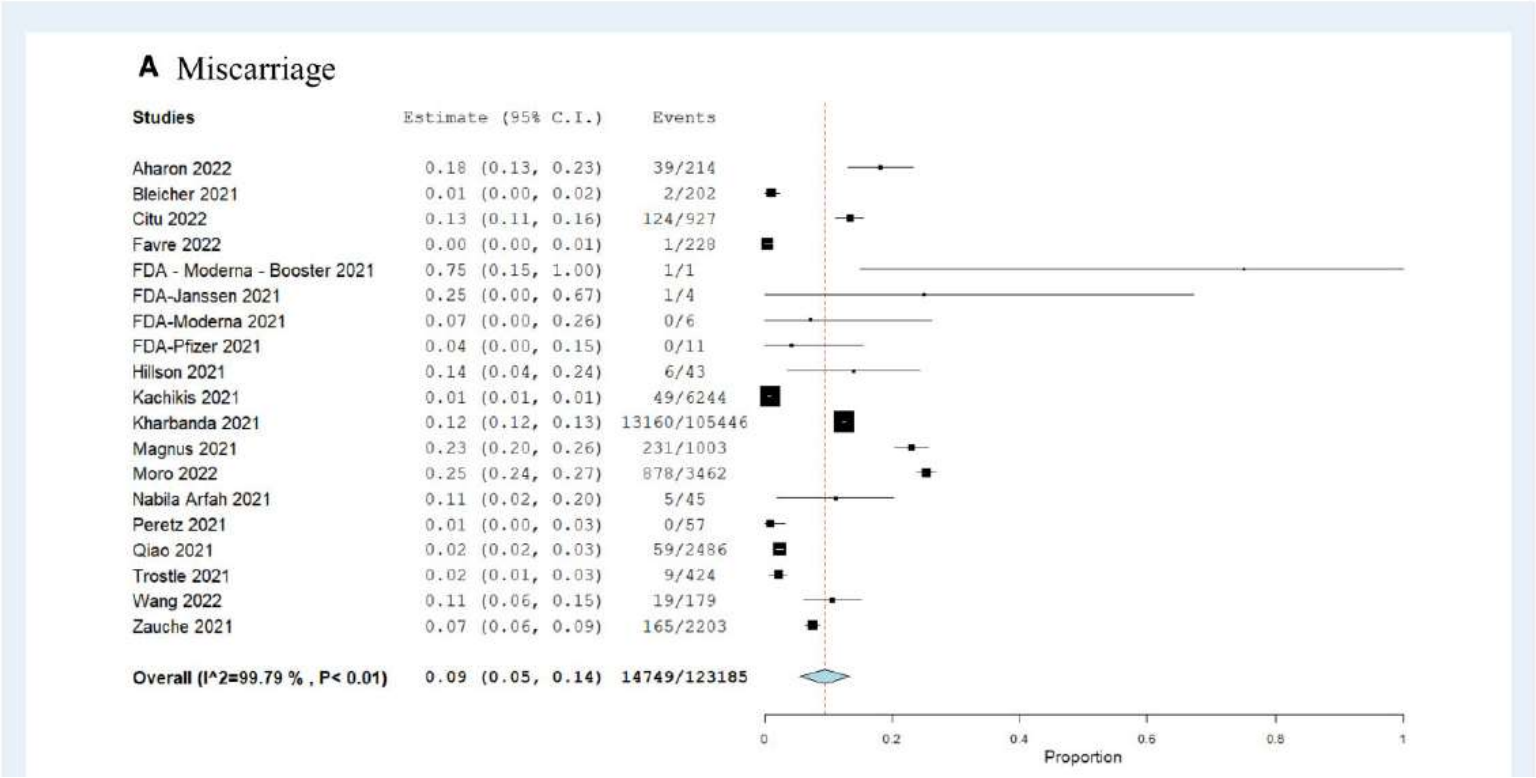
PARTICIPANTS/MATERIALS, SETTING, METHODS: We included observational and interventional studies that enrolled pregnant women and evaluated any of the available COVID-19 vaccines compared to placebo or no vaccination. We primarily reported on miscarriage in addition to ongoing pregnancy and/or live birth.

The risk of miscarriage following COVID-19 vaccination 2.

Table I Characteristics of included studies that evaluated the risk of miscarriage and rates of ongoing pregnancy/live birth among pregnant women who received a COVID-19 vaccine.

Study	Design	Countries	Funding source	Covid-19 vaccine	Vaccine doses	Inclusion criteria	Numbers analysed (n=)	Risk of bias
Aharon (2022)	Cohort	USA	Not stated	Pfizer, Moderna	2	Women undergoing fertility treatment who were vaccinated at least 14 days prior to starting medication for ovarian stimulation or a frozen-thawed embryo transfer cycle	2153	Moderate
Avraham (2022)	Cohort	Israel	No external funding	Pfizer	2	Women 20–42 years old undergoing IVF treatment cycles at a single centre	400	Moderate
Bleicher (2021)	Cohort	USA	Not stated	Pfizer	≥1	Being pregnant at enrolment and valid questionnaire	326	Serious
Bookstein Peretz (2021)	Case-control	Israel	Not stated	Pfizer	2	Pregnant women between 2 and 40 weeks' gestation who completed two doses of vaccine	57	Serious
Citu (2022)	Cohort	Romania	No external funding	Pfizer, Moderna	≥1	Women aged >18 years who were vaccinated during the first trimester of pregnancy	3094	Moderate
Favre (2022)	Cohort	Switzerland	Swiss Federal Office of Public Health and the CHUV Foundation	Pfizer, Moderna	≥1	Pregnant women with at least one injection between 1 week before last menstrual period to end of pregnancy	228	Moderate
FDA—Janssen (2021)	RCT	Brazil, Chile, Argentine, Colombia, Peru, Mexica, USA, South Africa	Janssen Research and Development	Janssen	1	Adults 18–59 years of age and 60 years of age or older, respectively, who were in good or stable health and did not have coexisting conditions that have been associated with an increased risk of severe COVID-19	8	Low
FDA—Moderna (2020)	RCT	USA	Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases	Moderna	2	18 years old and had no known history of SARS-CoV-2 infection and whose locations or circumstances put them at appreciable risk of acquiring SARS-CoV-2 infection or who were at high risk for severe disease (or both)	13	Low

The risk of miscarriage following COVID-19 vaccination 3.



The risk of miscarriage following COVID-19 vaccination 4.

MAIN RESULTS AND THE ROLE OF CHANCE: We included data from 21 studies (5 randomized trials and 16 observational studies) reporting on 149 685 women. The pooled rate of miscarriage among women who received a COVID-19 vaccine was 9% (n = 14 749/123 185, 95% CI 0.05–0.14). Compared to those who received a placebo or no vaccination, women who received a COVID-19 vaccine did not have a higher risk of miscarriage (risk ratio (RR) 1.07, 95% CI 0.89–1.28, I^2 35.8%) and had comparable rates for ongoing pregnancy or live birth (RR 1.00, 95% CI 0.97–1.03, I^2 10.72%).

LIMITATIONS, REASONS FOR CAUTION: Our analysis was limited to observational evidence with varied reporting, high heterogeneity and risk of bias across included studies, which may limit the generalizability and confidence in our findings.

WIDER IMPLICATIONS OF THE FINDINGS: COVID-19 vaccines are not associated with an increase in the risk of miscarriage or reduced rates of ongoing pregnancy or live birth among women of reproductive age. The current evidence remains limited and larger population studies are needed to further evaluate the effectiveness and safety of COVID-19 vaccination in pregnancy.

Opioid analgesia for acute low back pain and neck pain (the OPAL trial): a randomised placebo-controlled trial

*Caitlin M P Jones, Richard O Day, Bart W Koes, Jane Latimer, Chris G Maher, Andrew J McLachlan, Laurent Billot, Sana Shan, Chung-Wei Christine Lin, on behalf of the OPAL Investigators and Coordinators**

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This online publication has been corrected. The corrected version first appeared at thelancet.com

Summary

Background Opioid analgesics are commonly used for acute low back pain and neck pain, but supporting efficacy data are scarce. We aimed to investigate the efficacy and safety of a judicious short course of an opioid analgesic for acute low back pain and neck pain.

Methods OPAL was a triple-blinded, placebo-controlled randomised trial that recruited adults (aged ≥18 years) presenting to one of 157 primary care or emergency department sites in Sydney, NSW, Australia, with 12 weeks or less of low back or neck pain (or both) of at least moderate pain severity. Participants were randomly assigned (1:1) using statistician-generated, randomly permuted blocks to guideline-recommended care plus an opioid (oxycodone–

Opioid analgesic for acute low back pain and neck pain 1.

Research in context

Evidence before this study

We searched electronic databases MEDLINE (via Ovid), Embase (via Ovid), Cochrane Central Register of Controlled Trials and Systematic Reviews, and the WHO International Clinical Trials Registry Platform for trials or reviews published from database inception to June 9, 2022, which contained search terms "opioid", "placebo", and "low back" or "neck pain" or both (and synonyms). We assessed the quality of trials using the Cochrane ROB 1 tool and reviewed the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) ratings reported for the certainty of evidence in the systematic reviews. To our knowledge, there are no systematic reviews of opioid analgesics versus placebo for acute spinal pain. A previous review of opioids for spinal pain did not identify any studies on acute pain and found small to no effects of opioids on chronic pain. A review of opioids for acute musculoskeletal pain excluding back pain found that opioids had a small effect over placebo. We found three trials that had some degree of overlap with the OPAL trial. In one trial (low risk of bias) all participants received a non-steroidal anti-inflammatory drug besides an opioid or placebo. This trial found no benefit of adding opioids to non-steroidal anti-inflammatories. The second trial examined acute flares on chronic

Opioid analgesic for acute low back pain and neck pain 2.

neck pain, and the final trial had a short follow-up (2·5 days) and was industry sponsored. These trials reported moderate effects of opioids on pain but had high risk of bias.

Added value of this study

This study is not sponsored by industry and is the first placebo-controlled trial of an opioid analgesic, without the addition of another pain medicine, for acute low back and neck pain. The study reports data on the safety and efficacy of opioids up to the 12-month follow-up, as opposed to many other studies of opioids in acute and chronic low back pain and neck pain, which had short-term follow-ups only and used an enrichment design.

Opioid analgesic for acute low back pain and neck pain 3.

	Opioid (n=174)		Placebo (n=172)		Mean difference (95% CI)	p value
	n	Mean (SE)	n	Mean (SE)		
Pain severity (BPI-PS)						
Week 2	136	3·81 (0·19)	140	3·54 (0·19)	NA	NA
Week 4	127	3·08 (0·20)	122	2·73 (0·20)	NA	NA
Week 6	132	2·78 (0·20)	138	2·25 (0·19)	0·53 (–0·00 to 1·07)	0·051
Week 12	124	2·58 (0·20)	129	2·10 (0·19)	0·48 (–0·06 to 1·02)	0·083
Week 26	121	2·67 (0·20)	126	1·87 (0·19)	NA	NA
Week 52	123	2·37 (0·20)	128	1·81 (0·19)	0·57 (0·02 to 1·11)	0·041
Physical functioning, generic (BPI-IS)						
Week 2	126	3·90 (0·22)	132	3·58 (0·21)	NA	NA
Week 4	115	2·92 (0·22)	115	2·75 (0·22)	NA	NA
Week 6	125	2·64 (0·22)	126	2·12 (0·21)	0·52 (–0·08 to 1·12)	0·088
Week 12	114	2·48 (0·22)	120	1·90 (0·22)	0·58 (–0·03 to 1·19)	0·064
Physical functioning, back (RMDQ)						
Week 6	109	8·89 (0·64)	109	6·56 (0·64)	2·33 (0·55 to 4·11)	0·011
Physical functioning, neck (NDI), %						
Week 6	23	22·70% (3·66)	19	20·98% (3·93)	1·73 (–9·16 to 12·61)	0·75
Quality of life, physical score (SF-12v2)						
Week 2	119	39·24 (0·85)	125	40·00 (0·81)	NA	NA
Week 4	112	41·44 (0·86)	113	42·28 (0·84)	NA	NA
Week 6	119	43·78 (0·85)	117	44·62 (0·83)	–0·84 (–3·17 to 1·50)	0·48
Week 12	111	45·27 (0·86)	118	45·66 (0·82)	–0·40 (–2·74 to 1·95)	0·74
Quality of life, mental score (SF-12v2)						
Week 2	119	47·46 (0·87)	125	48·50 (0·82)	NA	NA
Week 4	112	48·65 (0·88)	113	50·46 (0·86)	NA	NA
Week 6	119	48·01 (0·86)	117	51·26 (0·85)	–3·25 (–5·63 to –0·87)	0·0075
Week 12	111	48·24 (0·88)	118	51·91 (0·84)	–3·67 (–6·07 to –1·27)	0·0028
Global perceived effect scale						
Week 2	121	1·22 (0·23)	126	1·76 (0·23)	NA	NA
Week 4	114	1·81 (0·24)	114	1·93 (0·24)	NA	NA
Week 6	121	2·01 (0·23)	119	2·16 (0·23)	–0·15 (–0·80 to 0·50)	0·65
Week 12	111	2·27 (0·24)	119	2·46 (0·23)	–0·19 (–0·85 to 0·47)	0·58

For all outcomes, higher scores reflect worse outcomes except for quality of life (mental and physical) and global perceived effect, for which higher scores reflect better outcomes. BPI-PS=Brief Pain Inventory Pain Severity. BPI-IS=Brief Pain Inventory Interference Subscale. NA=not applicable. NDI=Neck Disability Index. RMDQ=Roland Morris Disability Questionnaire. SE=standard error.

Table 2: **Model results for primary and secondary outcomes**

Opioid analgesic for acute low back pain and neck pain 4.

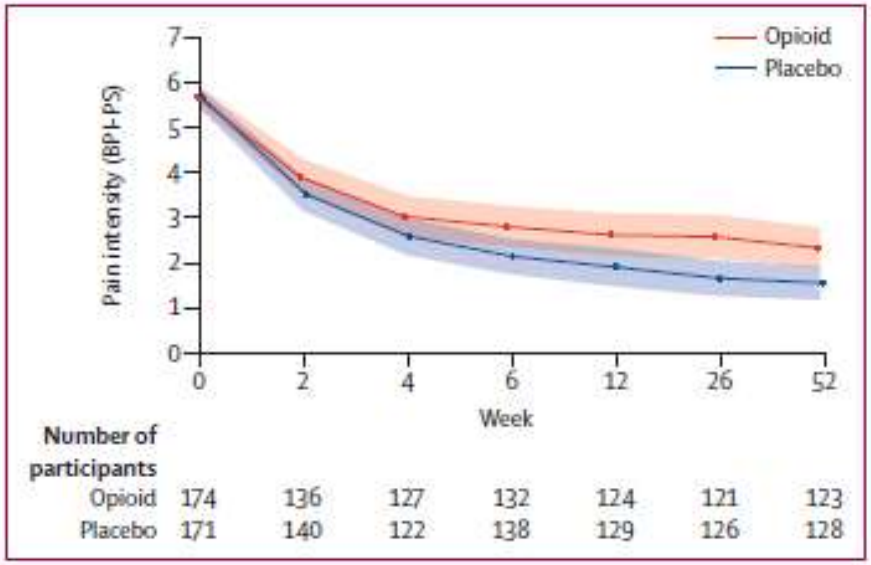

Figure 2: **Longitudinal plot of mean pain severity score**
Datapoints show mean scores at each timepoint, and the shaded areas show 95% CIs. Estimates are raw values (not modelled). BPI-PS=Brief Pain Inventory, pain severity subscale.

Opioid analgesic for acute low back pain and neck pain 5.

Implications of all the available evidence

Our findings support the results from other studies and reviews on similar populations, which found that the effects of opioids on back and neck pain, and musculoskeletal pain in general, were probably small to none. Our findings also go further to say that not only are opioids not going to benefit individuals with back and neck pain, but they might also cause worse outcomes even after short-term judicious use.

The legacy effect of hyperglycemia and early use of SGLT-2 inhibitors: a cohort study with newly-diagnosed people with type 2 diabetes

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Summary

Background A delay in reaching HbA1c targets in patients with newly-diagnosed type 2 diabetes (T2D) is associated with an increased long-term risk of developing cardiovascular diseases (CVD), a phenomenon referred to as legacy effect. Whether an early introduction of glucose-lowering drugs with proven benefit on CVD can attenuate this phenomenon is unknown.

Methods Using data derived from a large Italian clinical registry, *i.e.* the AMD Annals, we identified 251,339 subjects with newly-diagnosed T2D and without CVD at baseline. Through Cox regressions adjusted for multiple risk factors, we examined the association between having a mean HbA1c between 7.1 and 8% or >8% compared with ≤7% for

Hyperglycemia - SGLT2 inhibitors 1.

Research in context

Evidence before this study

Data from historic clinical trials and the subsequent observational follow-ups such as the UKPDS and the DCCT/EDIC, as well as large observational studies such as the Diabetes & Aging study, suggest that a poor glycemic control in patients with early-stage diabetes increases the long-term risk of macrovascular complications, a phenomenon known as the legacy effect. However, such studies were conducted when glucose-lowering drugs with proven cardiovascular benefit, *e.g.*, the SGLT-2i, were not available.

Added value of this study

With this study we substantiate the evidence that poor glycemic control after the diagnosis of type 2 diabetes is associated with an increased cardiovascular risk during the subsequent follow-up. However, we show also that the introduction of an SGLT-2i during the first two years after

Hyperglycemia - SGLT2 inhibitors 2.

diabetes diagnosis eliminated the association between poor glycemic control and the later development of cardiovascular events, measured as a composite of myocardial infarction, stroke, coronary or peripheral revascularization, and coronary or peripheral bypass.

Implications of all the available evidence

While the results of this study need confirmation in independent and prospective cohorts, they might suggest that SGLT-2i could attenuate the deleterious long-term damage promoted by poor glycemic control in the first years after diabetes diagnosis. Thus, while reaching the HbA1c target as soon as possible remains the main therapeutic goal in early diabetes management, the introduction of SGLT-2i might be considered an option for those patients unable to attain rapidly the recommended HbA1c target.

Hyperglycemia - SGLT2 inhibitors 3.

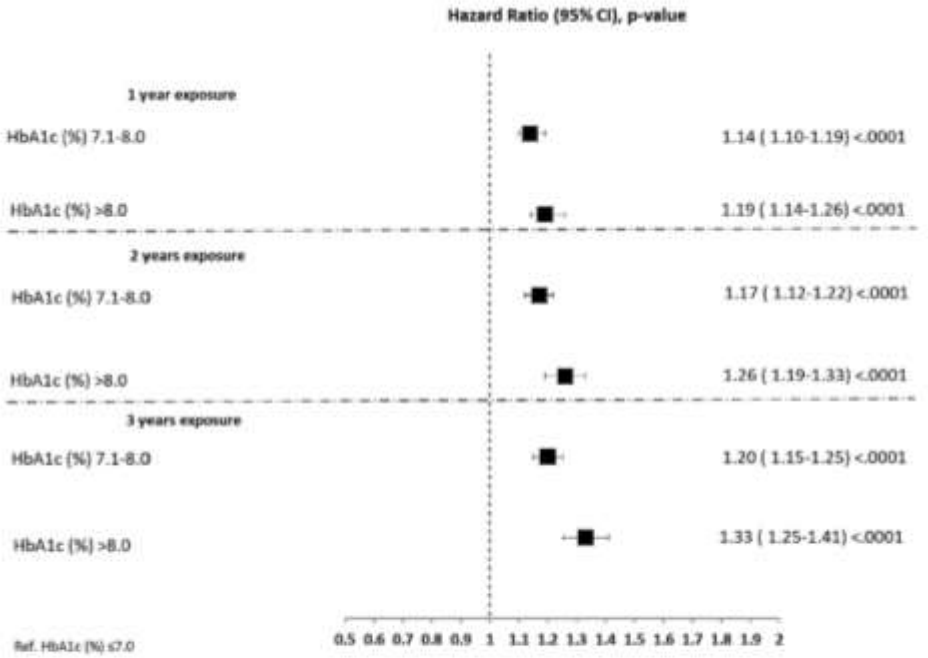


Fig. 3: **Poor, early glycemic control and the subsequent risk of cardiovascular diseases.** Pseudo-forest plot showing the adjusted hazard ratios (HR) with the relative 95% confidence interval (CI) and the p value, derived from the Cox regression analyses exploring the associations between glycemic control and the risk of the CVD at follow-up in the whole cohort according to the degree of glycemic control in the three exposure periods assessed. HbA1c $\leq$ 7% is the reference.

Hyperglycemia - SGLT2 inhibitors 4.

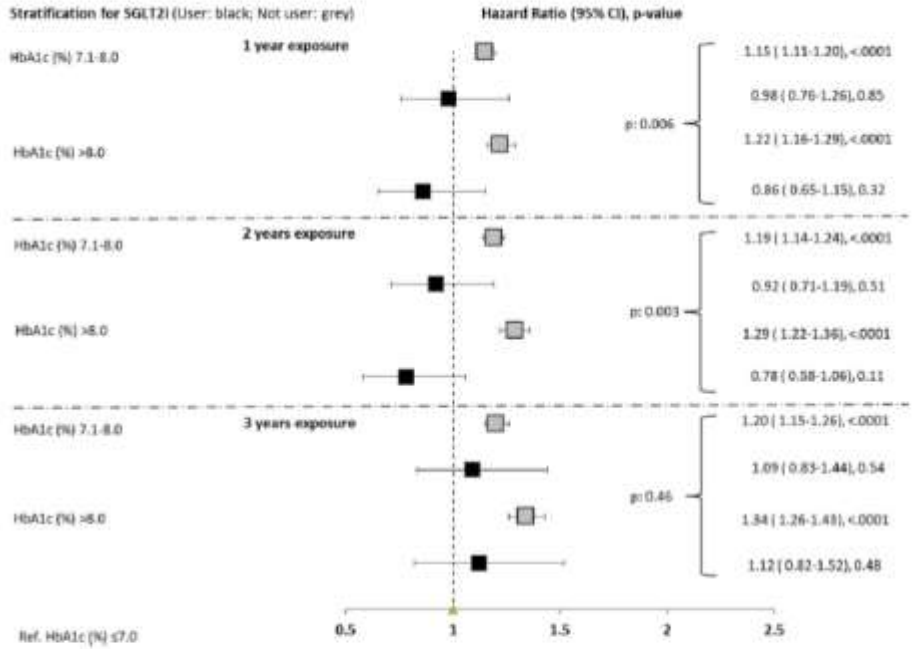
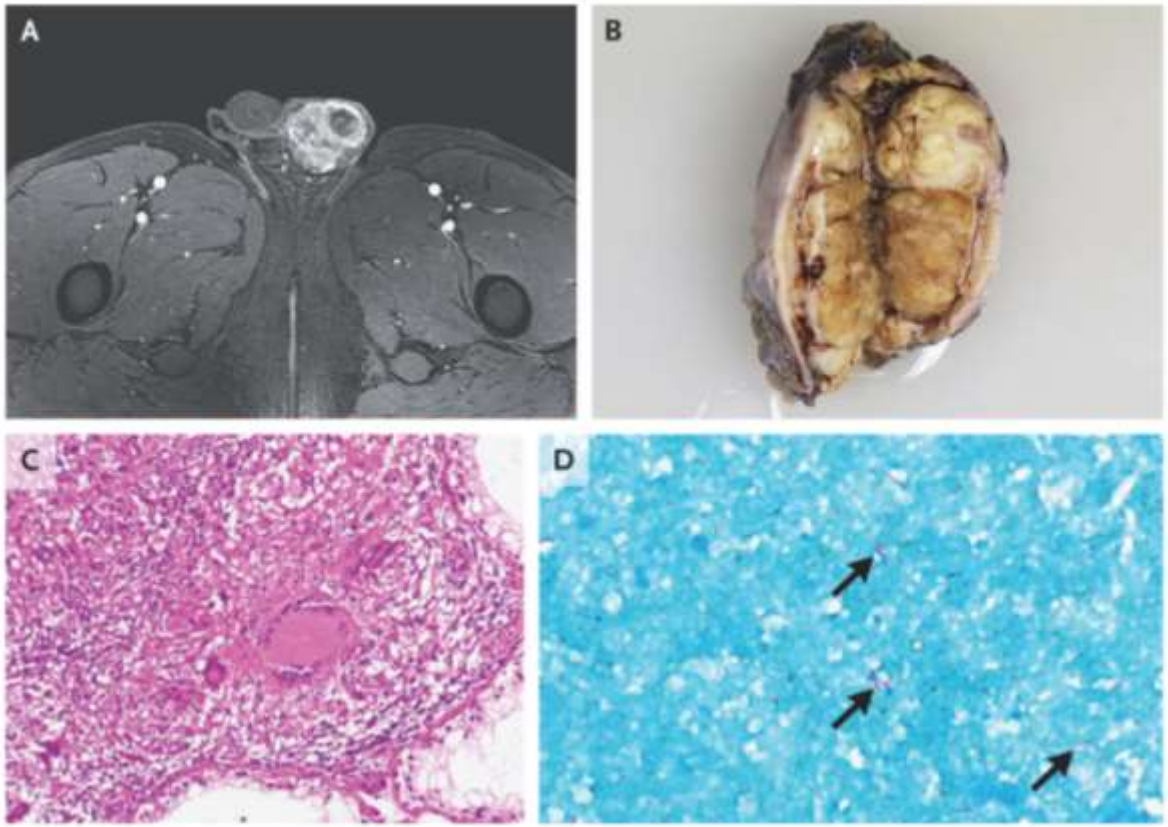


Fig. 4: **Early introduction of SGLT-2i attenuate metabolic memory.** Pseudo-forest plot showing the adjusted hazard ratios (HR) with the relative 95% confidence interval (CI) and the p value, derived from the Cox regression analyses exploring the associations between glycemic control and the risk of the CVD at follow-up in patients stratified according to use of SGLT-2i during the exposure phase or not users, in the three exposure periods assessed. HbA1c ≤ 7% is the reference.

Testicular cancer ?

August 24, 2023
N Engl J Med 2023; 389:e13
DOI: 10.1056/NEJMicm2301695
Metrics



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Metrics

A 42-year-old man presented to the urology clinic with a 2-month history of painless enlargement of the left testicle. He reported no fevers, night sweats, weight loss, respiratory symptoms, or urethral discharge. The physical examination was notable for an enlarged, firm, nontender left testicle. Magnetic resonance imaging of the pelvis showed a lobulated left testicular mass with heterogeneous enhancement (Panel A). Testing for serum tumor markers for testicular cancer was negative. Owing to concern about testicular cancer, a radical inguinal orchiectomy was performed. Gross examination of the excised testis showed necrotic nodules (Panel B), and histopathological examination showed granulomatous inflammation with caseous necrosis (Panel C) and acid-fast bacilli (Panel D, arrows). A real-time–polymerase-chain-reaction assay identified *Mycobacterium tuberculosis*. Computed tomography of the chest was normal. A diagnosis of testicular tuberculosis was made. A 9-month course of antituberculosis therapy was prescribed. At follow-up 1 year after the initial presentation, the patient was in good health.

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