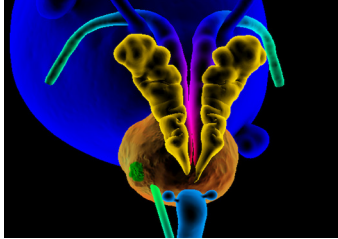


# research



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## ORIGINAL RESEARCH Population based study

### Prostate cancer incidence and mortality in Europe and implications for screening activities

Vaccarella S, Li M, Bray B, et al

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**Study question** What is the epidemiological landscape of prostate cancer in Europe, and what are the implications for the recently proposed EU screening initiatives?

**Methods** Data from 26 European countries (men aged 35-84) on prostate cancer incidence (until 2017) were obtained from the International Agency for Research on Cancer and mortality data from WHO (until 2020). Information on PSA testing trends was available for 12 countries. Annual age standardised rates of prostate cancer incidence and mortality per 100 000 men were calculated using the world standard population as a reference.

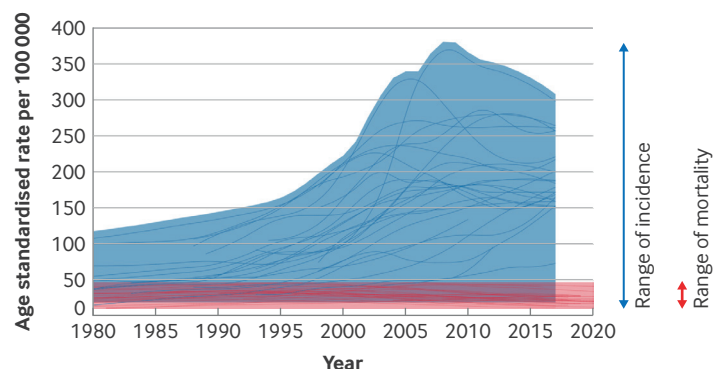
**Study answer and limitations** Over the past decades, incidence rates for prostate cancer varied markedly in magnitude and rate of change, in parallel with temporal variations in PSA testing. The variation in incidence across countries was largest around the mid-2000s, with rates spanning

from 46 (Ukraine) to 336 (France) per 100 000 men. Thereafter, incidence started to decline in several countries, but with the latest rates nevertheless remaining raised and increasing again in the most recent quinquennium in several countries. Mortality rates during 1980-2020 were lower and less variable than incidence rates, with steady declines in most countries and lesser temporal differences between countries. Overall, the up to 20-fold variation in prostate cancer incidence contrasts with a corresponding fivefold variation in mortality. Limitations include lack of data on cancer stage and treatment modalities, and heterogeneous information on temporal changes in PSA testing.

**What this study adds** The findings of this study suggest that the

epidemiological characteristics of prostate cancer in the European countries included, particularly the contrast between large heterogeneity in incidence trends and the more uniform reduction in mortality, are compatible with substantial overdiagnosis, driven by the highly variable patterns of PSA testing. Future activities on prostate cancer screening must be carefully designed, implemented, and monitored so as to minimise the harms of overdiagnosis.

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Range of age standardised incidence and mortality rates of prostate cancer per 100 000 men aged 35-84 years over time among the included European countries. Lines are smoothed by the Loess regression algorithm (bandwidth: 0.4)

# SGLT-2 inhibitors and dementia

**ORIGINAL RESEARCH** Population based cohort study

## Risk of dementia after initiation of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors in adults aged 40-69 years with type 2 diabetes

Shin A, Koo BK, Lee JY, Kang EH

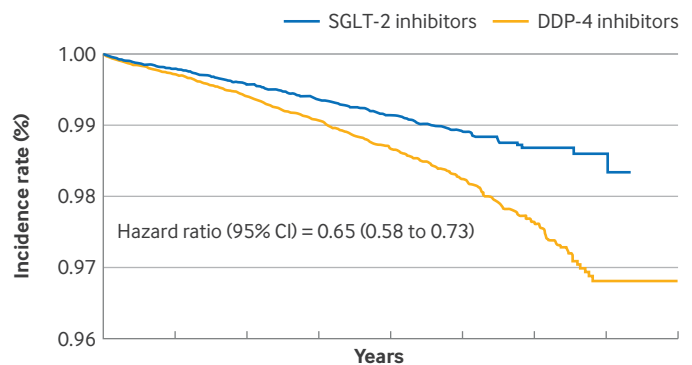
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**Study question** What is the risk of dementia associated with sodium-glucose cotransporter-2 (SGLT-2) inhibitors compared with dipeptidyl peptidase-4 (DPP-4) inhibitors among adults aged 40-69 years with type 2 diabetes mellitus?

**Methods** This population based cohort study longitudinally followed up adults aged 40-69 years with type 2 diabetes mellitus in Korea who initiated either an SGLT-2 inhibitor or a DPP-4 inhibitor and were 1:1 matched on propensity score from the day they initiated the study drug until the development of dementia, treatment discontinuation, death, or end of database (31 December 2021). The primary outcome was new onset dementia. The incidence rate of dementia was calculated in the two treatment groups, and the risk was compared using hazard ratios and corresponding 95% confidence intervals (CIs) estimated by Cox models. Control outcomes were genital infections (positive), and osteoarthritis related clinical encounters, and cataract surgery (negative).

**Study answer and limitations** 110 885 propensity score matched pairs of initiators of an SGLT-2 inhibitor or a DPP-4 inhibitor were followed-up for a mean 670 (standard deviation 650) days, generating 1172 people with newly diagnosed dementia: incidence rate 0.22 per 100 person years in initiators of SGLT-2 inhibitors and 0.35 per 100 person years in initiators of DPP-4 inhibitors, with hazard ratios of 0.65 (95% CI 0.58 to 0.73) for dementia, 0.54 (0.46 to 0.63) for dementia requiring drugs, 0.61 (0.53 to 0.69) for Alzheimer's disease, and 0.48 (0.33 to 0.70) for vascular dementia. The hazard ratios for the control outcomes were 2.67 (2.57 to 2.77) for genital infections, 0.97 (0.95 to 0.98) for osteoarthritis related encounters, and 0.92 (0.89 to 0.96) for cataract surgery.



**No at risk**

DPP-4 inhibitors

110 885 64 159 44 452 29 171 18 856 10 149 4 122 878 2

SGLT-2 inhibitors

110 885 56 999 36 536 22 355 13 561 6 827 2 587 289 0

**Kaplan-Meier curves for dementia-free survival comparing propensity score matched initiators of SGLT-2 inhibitors versus DPP-4 inhibitors. CI=confidence interval; DPP-4=dipeptidyl peptidase-4; SGLT-2=sodium-glucose cotransporter-2**

When calibrated for residual confounding measured by cataract surgery, the hazard ratio for dementia was 0.70 (0.62 to 0.80). The association was greater for more than two years of treatment than for two years or less and persisted across subgroups. Common delay of dementia diagnoses in the real world setting could have introduced misclassification bias on the exact date of dementia occurrence. As this study was observational and therefore prone to residual confounding and informative censoring, the effect size could have been overestimated. Causality should be confirmed in a randomised controlled trial.

**What this study adds** SGLT-2 inhibitors are associated with a lower risk of dementia.

**Funding, competing interests, and data sharing** Supported by a grant from the Korea Health Industry Development Institute (KHIDI)-AZ Diabetes Research Program. No competing interests declared. Patient level data are not publicly allowed according to data use agreement.

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## COMMENTARY New evidence links these agents to lower dementia risk in adults with type 2 diabetes

Dementia remains a profound global health challenge. According to a report from the World Health Organization, more than 55 million people worldwide currently have dementia, and each year the disease is diagnosed in around 10 million people.<sup>1</sup> This neurological disorder, characterised by the progressive deterioration of cognitive function, continues to elude effective treatment. Notably, type 2 diabetes is recognised as an important modifiable risk factor for dementia, contributing to both Alzheimer's disease and vascular dementia.<sup>2</sup> Recent evidence suggests that certain antidiabetic drugs, specifically sodium-glucose cotransporter-2 (SGLT-2) inhibitors, may offer neuroprotective benefits beyond their glucose lowering effects, thereby adding a promising dimension to dementia prevention strategies.<sup>3-5</sup>

The study by Shin and colleagues sheds light on this potential benefit by analysing data from the Korean National Health Insurance Service.<sup>6</sup> These authors compared the risk of dementia associated with SGLT-2 inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors in 110 885 propensity score matched pairs of adults with type 2 diabetes aged 40-69 years. The study included those starting treatment with an SGLT-2 inhibitor who had a considerably lower incidence of dementia than those starting treatment with a DPP-4 inhibitor, over a mean follow-up of 670 days (0.22 v 0.35 per 100 person years; hazard ratio 0.65, 95% confidence interval (CI) 0.58 to 0.73). These findings indicate a 35% relative reduction in overall dementia risk among SGLT-2 inhibitor users.

The risk reduction associated with SGLT-2 inhibitors was consistently observed across different types of dementia, including Alzheimer's disease (hazard ratio 0.61, 95% CI 0.53 to 0.69) and vascular dementia (0.48, 0.33 to 0.70). Additionally, the effect seemed more pronounced with longer treatment duration. These findings extend current knowledge about the potential pleiotropic effects of SGLT-2 inhibitors on



FRANCIS JOSEPH DEAN/ALAMY

### The study suggests a possible repurposing of SGLT-2 inhibitors for dementia prevention

neurodegenerative diseases, in addition to their known metabolic and cardiorenal benefits.<sup>7</sup>

#### Study strengths

Shin and colleagues successfully showed how to use a large scale secondary healthcare database to explore clinically important questions that have yet to be evaluated or are difficult to evaluate through randomised controlled trials. The authors used rigorous pharmacoepidemiological approaches, such as applying a target trial emulation framework,<sup>8</sup> using an active comparator new user design,<sup>9</sup> and utilising propensity score methods to control for confounders.<sup>10</sup> These methods helped avoid biases common to observational studies, thereby strengthening the ability to draw causal inference from observational data.<sup>8</sup> Various subgroup analyses and sensitivity analyses, along with positive and negative control outcome analyses, also support the robustness of the study findings.

The possible mechanisms driving the lower risk of dementia observed with SGLT-2 inhibitors are multifaceted. SGLT-2 inhibitors reduce hyperglycaemia, improve insulin resistance, decrease oxidative stress and inflammation, and provide cardiovascular and renal benefits, all of which are key contributors to the development of dementia in adults with type 2 diabetes.<sup>4,5</sup> Additionally, preclinical studies have suggested that SGLT-2 inhibitors are linked to the amelioration of amyloid  $\beta$  deposition and tau protein phosphorylation, which are considered major pathogenetic mechanisms of Alzheimer's disease.<sup>4,5</sup>

Some limitations of Shin and colleagues' study should be noted. Several factors, such as participants' serum glucose levels, disease severity, over-the-counter drug use, and lifestyle behaviours, were not included in the analyses, leaving the possibility of residual or unmeasured confounding. In addition, the relatively short mean follow-up period of 670 days may make this study susceptible to informative censoring, reverse causation, and outcome misclassification, potentially leading to overestimation of the results.

#### Practical implications

Shin and colleagues' findings have important implications for clinical practice as well as from a public health perspective. For people with type 2 diabetes, the potential reduction in dementia incidence with SGLT-2 inhibitor treatment offers important additional clinical benefits beyond the known glucose lowering effects and other cardiorenal protections. For clinicians, these findings emphasise the need to integrate considerations about cognitive health into diabetes management strategies, potentially supporting early use of SGLT-2 inhibitors for people at risk of dementia.

For researchers, the new findings indicate a need for randomised controlled trials to confirm these observational results. Additional studies are also needed to explore the underlying mechanisms of any neuroprotective effects of SGLT-2 inhibitors. Clinical guidelines and healthcare policies should be updated regularly to incorporate latest best evidence on the potential benefits of SGLT-2 inhibitors, including reduced dementia risk, given the substantial socioeconomic and public health burdens associated with both dementia and type 2 diabetes.

As no cure currently exists for dementia, and few effective treatment options are available, strategies that can potentially prevent onset are critically important. Although further randomised controlled trials are urgently needed to confirm these findings, Shin and colleagues' study reports promising results and suggests a possible repurposing of SGLT-2 inhibitors for dementia prevention in people with type 2 diabetes.

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# Long term exposure to road traffic noise and air pollution and risk of infertility in men and women

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**Study question** Is long term residential exposure to road traffic noise and particulate air pollution associated with infertility in men and women?

**Methods** This nationwide cohort study included 526 056 men and 377 850 women aged 30-45 with fewer than two children who were cohabiting or married and residing in Denmark from 2000 to 2017. The main outcome was incident infertility in men and women during follow-up to 31 December 2017 in the Danish National Patient Register. Long term exposure to road traffic noise and particulate matter with a diameter <2.5 µm (PM<sub>2.5</sub>) were modelled at all participants' residential addresses, taking address history into account. Cox proportional hazards models were applied to estimate associations (hazard ratios) between these exposures and risk of infertility in men



PAUL BALDESARE/ALAMY

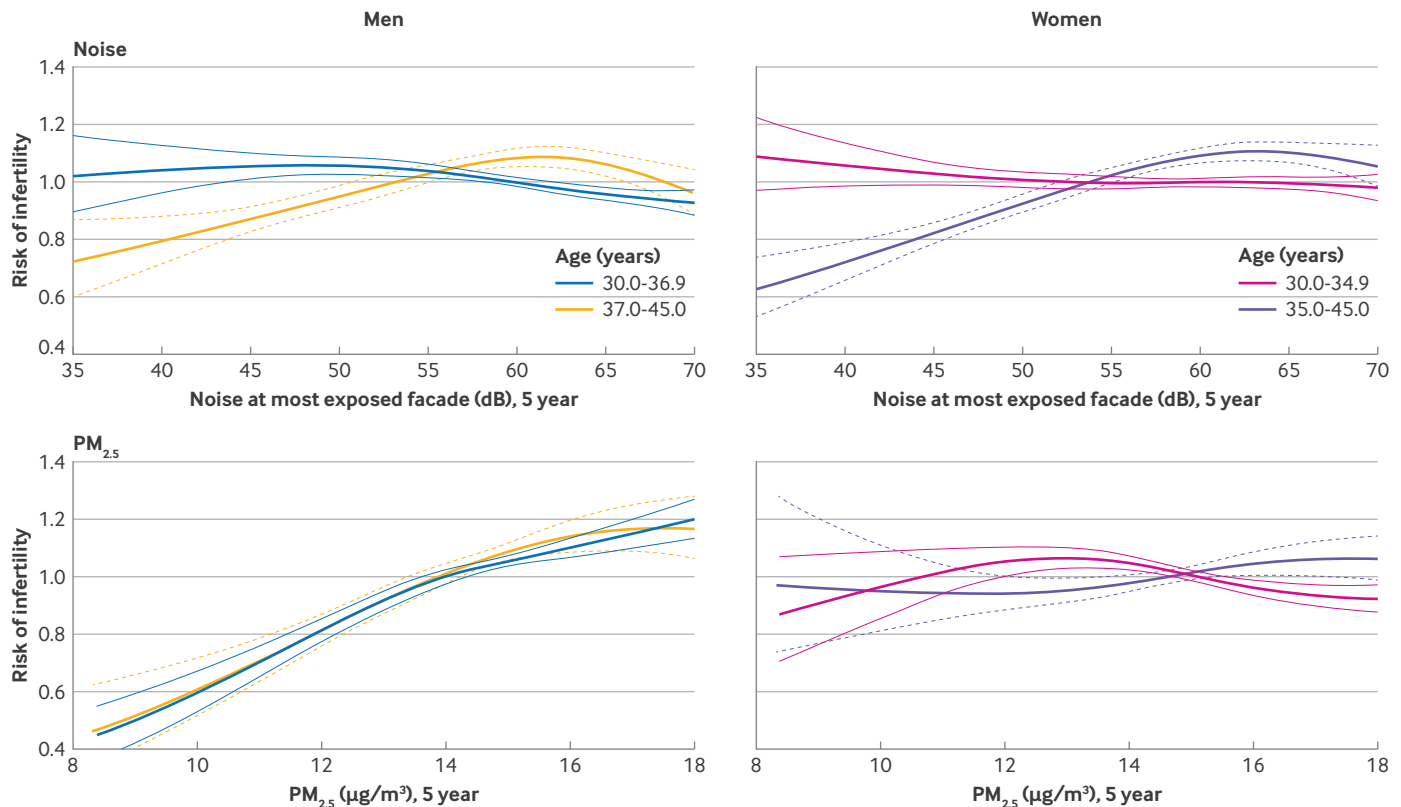
and women with adjustment for various sociodemographic variables, including education and income.

**Study answer and limitations** Infertility was diagnosed in 16 172 men and 22 672 women during a mean follow-up of 4.3 years and 4.2 years, respectively. Mean exposure to PM<sub>2.5</sub> over five years was strongly associated with risk of infertility in men, with hazard ratios of 1.24 (95% confidence interval 1.18 to 1.30) among men aged 30-36.9 and 1.24 (1.15 to 1.33) among men aged 37-45 for each interquartile (2.9 µg/m<sup>3</sup>) higher PM<sub>2.5</sub> after adjustment for sociodemographic variables and road traffic noise. PM<sub>2.5</sub> was not associated with infertility in women. Road traffic noise (Lden, most exposed facade of residence) was associated with a higher risk of infertility among women aged 35-45 (hazard ratio of 1.14 (1.10 to 1.18)

for each interquartile (10.2 dB) higher five year mean exposure). Noise was not associated with infertility among younger women (30-34.9). In men, road traffic noise was associated with higher risk of infertility among those aged 37-45 (1.06, 1.02 to 1.11), but not among those aged 30-36.9 (0.93, 0.91 to 0.96). A study limitation is that although the study population was restricted to people who were likely at risk of an infertility diagnosis, it was inevitable that couples not actively trying to conceive were also included, possibly biasing the results.

**What this study adds** PM<sub>2.5</sub> was associated with a higher risk of an infertility diagnosis in men, whereas road traffic noise was associated with a higher risk of an infertility diagnosis in women older than 35 years, and potentially in men older than 37 years. If these results are confirmed in future studies, higher fertility could be added to the list of health benefits from regulating noise and air pollution.

**Funding, competing interests, and data sharing** No funding received. No competing interests declared. Data are based on Danish national registers, belonging to the Danish Ministry of Health and Statistics Denmark, and the authors are therefore not allowed to share raw data.



Splines showing association between five year mean residential exposure to road traffic noise at the most exposed facade at home and PM<sub>2.5</sub> and risk of infertility in men and women in groups according to age in the fully adjusted model 3. dB=decibel; PM<sub>2.5</sub>=fine particulate matter with a diameter <2.5 µm