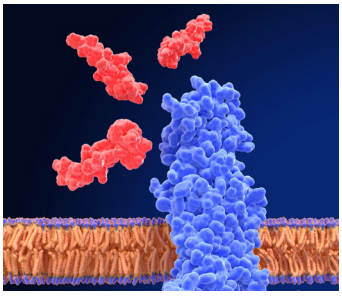
research

Future burden of Parkinson's disease p 245



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Projecting Parkinson's disease burden

ORIGINAL RESEARCH Modelling study of Global Burden of Disease Study 2021

Projections for prevalence of Parkinson's disease and its driving factors in 195 countries and territories to 2050

Su D, Cui Y, He C, et al

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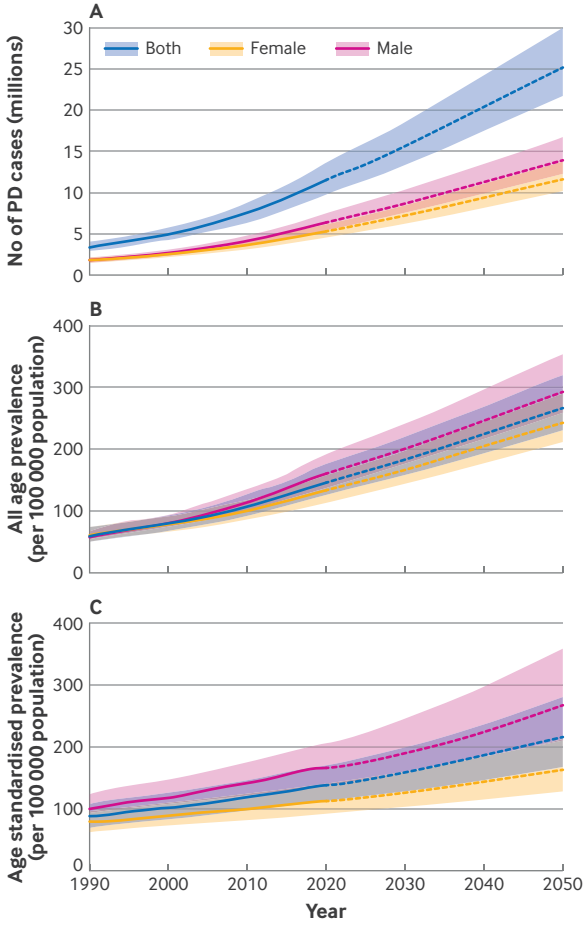
Study question What will the global, regional, and national prevalence of Parkinson's disease be in 2050, and what factors will drive the projected changes?

Methods This modelling study was based on data from the Global Burden of Disease (GBD) Study 2021. An ensemble of models was used to incorporate six projection models, each using the regression method, to project the number of cases, all age prevalence, and age standardised prevalence of Parkinson's disease in 2050. The contributions of population ageing, population growth, and changes in prevalence to the increase in Parkinson's disease cases were examined.

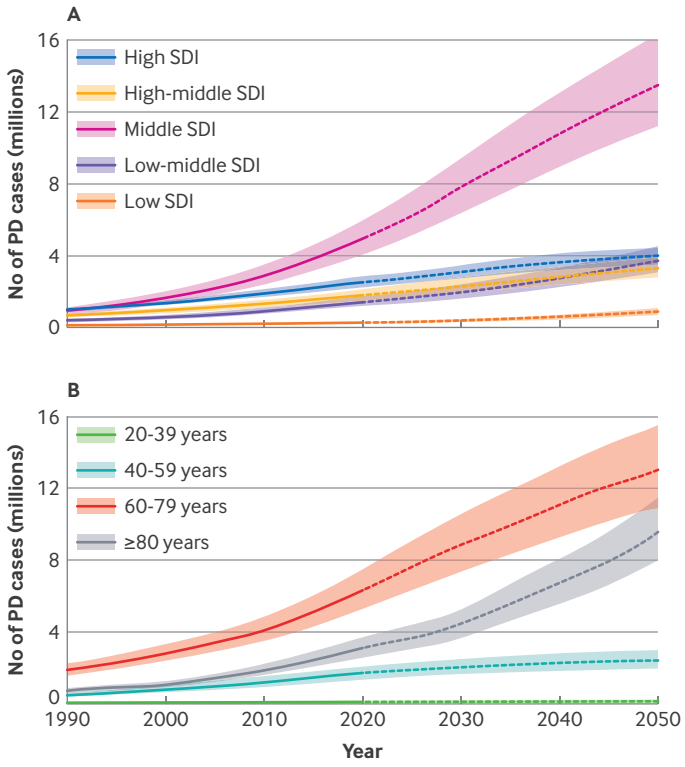


Estimated trends in global number of Parkinson's disease (PD) cases (A), all age prevalence of PD (B), and age standardised prevalence of PD (C), with 95% uncertainty intervals, 1990-2050. Solid lines represent values from Global Burden of Disease Study (1990-2021); dotted lines represent projected values (2022-50)

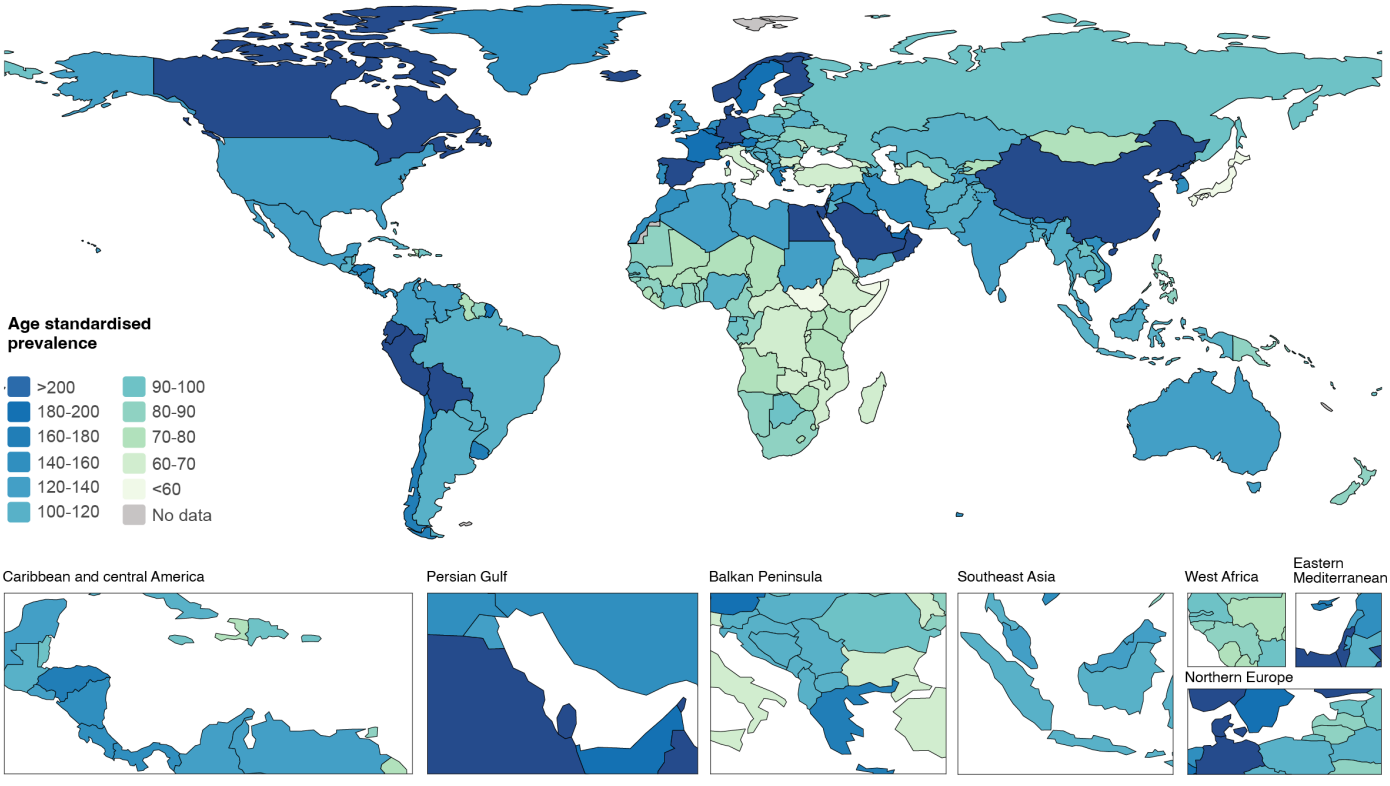
Study answer and limitations Globally, the number of Parkinson's disease cases in 2050 was estimated to be 25.2 million, an increase of 112% from 2021. The age standardised prevalence was estimated to be 216 cases per 100 000 in 2050, an increase of 55% from 2021. Countries in the middle fifth of Socio-demographic Index were projected to have the most substantial rise in both all age and age standardised prevalence of Parkinson's disease between 2021 and 2050. The GBD East Asia region was projected to have the highest number of Parkinson's disease cases in 2050. Population ageing (89%) was forecast to be the primary contributor to the growth in Parkinson's disease cases from 2021 to 2050, followed by population growth (20%) and changes in prevalence (3%). The male-to-female ratio in age standardised prevalence was expected to rise. However, the limited availability of data in countries with low Socio-demographic Index may affect the predictions.

What this study adds By 2050, Parkinson's disease is projected to pose a greater public health challenge, particularly in middle Socio-demographic Index countries, in the GBD East Asia region, and among men. Population ageing will be the primary driver of this increase.

Funding, competing interests, and data sharing The study was funded by the National Nature Science Foundation of China. The authors have no competing interests to declare. A technical appendix with details on the formula and calculations for the bayesian model averaging model is available at https://github.com/hechzh/Prevelance-2024-080952/tree/master.



Estimated trends of numbers of Parkinson's disease (PD) cases by Sociodemographic Index (SDI) fifths (top) and age groups (bottom), for both sexes combined, with 95% uncertainty intervals, 1990-2050. Solid lines represent values from Global Burden of Disease (1990-2021); dotted lines represent projected values (2022-50)



Projected age standardised prevalence (per 100 000) of Parkinson's disease in 2050, by country and territory for both sexes combined

Parkinson's disease is a considerable health problem owing to its high and rising global prevalence, its progressively degenerative nature, and its wide range of symptoms. In 2019 more than 8.5 million people worldwide were living with Parkinson's disease, a number that has more than doubled in the past 25 years.[1] Parkinson's disease has a severe impact on individuals and their families, including social consequences and economic costs.[2] Tackling this complex disease requires a multifactorial approach including increased awareness, improved diagnostics, better treatments, and ongoing research to find a cure.

Projecting the future number of people with Parkinson's disease is important for several reasons. Accurate projections enable appropriate allocation of healthcare resources and a better understanding of demand for specialists, drug treatments, rehabilitation, and long term care, preventing shortages that could lead to delayed diagnoses, inadequate treatment choices, and diminished health related quality of life for patients. Projections also inform targeted interventions, early diagnosis efforts, and public health prevention and management strategies.

What does the study tell us?

The modelling study of Su and colleagues projects a substantial increase in Parkinson's disease cases globally by 2050, reaching 25 million individuals, a doubling from 2021.[4] Population ageing was identified as the primary driver, followed by population growth. The overall prevalence is predicted to increase by 76%, and age standardised prevalence will also rise by 55%. The study reports that the largest increases will occur in East Asia and among the oldest age group (≥80 years). It also highlights differences by Socio-demographic Index, a composite measure of development based on income per capita, educational attainment, and fertility rates. The Socio-demographic Index is widely used in global health research to assess how social and economic factors influence disease burden.[5] The study also estimates the impact of lifestyle factors on future Parkinson's disease prevalence by using population attributable fractions.[4] It suggests that increasing physical activity could reduce the number of cases, whereas smoking cessation may lead to a rise in prevalence. The study concludes that Parkinson's disease will pose a greater public health challenge by 2050, emphasising the need for increased research, informed policies, and resource allocation.

AMELIE-BENOIST/BSIP/SPL

Parkinson's disease will pose a greater public health challenge by 2050

Making reliable projections

Given the resource and policy implications, modelling of future disease burden must mirror what might happen in reality as closely as possible. Researchers need to consider several methodological factors when projecting future case numbers of chronic conditions that may allow for more accurate estimates. Some researchers are now moving beyond simple extrapolation of prevalence to use the more robust illness-death model.[6] Prevalence extrapolation is limited because it assumes that current prevalence patterns will remain unchanged. It ignores key factors such as changes in disease incidence (new cases) and mortality rates among individuals with and without Parkinson's disease. As prevalence results from a complex interplay between incidence and mortality, failing to account for these dynamics can lead to misleading projections.[7]

By contrast, the illness-death model provides a more accurate representation of disease dynamics by incorporating transitions between different health states. Specifically, it models movement from a healthy state to Parkinson's disease, from a healthy state to death (without developing Parkinson's disease), and from Parkinson's disease to death. By explicitly accounting for these transitions, projections based on the illness-death model are more realistic and better suited for long term healthcare planning. The advantage of this approach has been shown in a recent study comparing different projection methods for another age related chronic disease.[8] The study found that prevalence extrapolation substantially underestimates future case numbers, failing to capture the increasing incidence and evolving mortality trends. Given that Su and colleagues used prevalence extrapolation in their Parkinson's disease projections, their estimates are likely to be similarly underestimated.

The estimates of population attributable fraction rely on strong causal assumptions, implying that modification of risk factors directly translates to proportional changes in disease burden. However, such estimates often oversimplify complex disease processes, ignoring factors such as incomplete risk factor elimination, latency periods, and real world feasibility of interventions.[9] Although population impact fractions attempt to overcome this by modelling partial exposure reductions, they still assume that intervention effects mirror observational associations, which may not hold as a result of confounding, reverse causation, or effect heterogeneity.[10] More robust causal modelling is needed to produce realistic and actionable projections.

Although the projections by Su and colleagues highlight an urgent public health challenge,[4] more methodologically advanced approaches that integrate incidence and mortality dynamics—such as the illness-death model—allow for better forecasting and ensure that healthcare systems, policy makers, and researchers are equipped with reliable data for long term planning. As Parkinson's disease cases are expected to rise sharply, adopting rigorous modelling techniques is essential to guide resource allocation, inform policy decisions, and advance research efforts. Future projections should prioritise methods that capture the true complexity of chronic disease progression, ultimately leading to more effective interventions and improved patient outcomes.

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GLP-1 receptor agonists and suicidality

ORIGINAL RESEARCH Active comparator, new user cohort study

Glucagon-like peptide-1 receptor agonists and risk of suicidality among patients with type 2 diabetes

Shapiro SB, Yin H, Yu OHY, Rej S, Suissa S, Azoulay L

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Study question Do patients with type 2 diabetes using a glucagon-like peptide-1 (GLP-1) receptor agonist have an increased risk of suicidal ideation, self-harm, or suicide compared with patients using a dipeptidyl peptidase-4 (DPP-4) inhibitor or a sodium-glucose cotransporter-2 (SGLT-2) inhibitor?

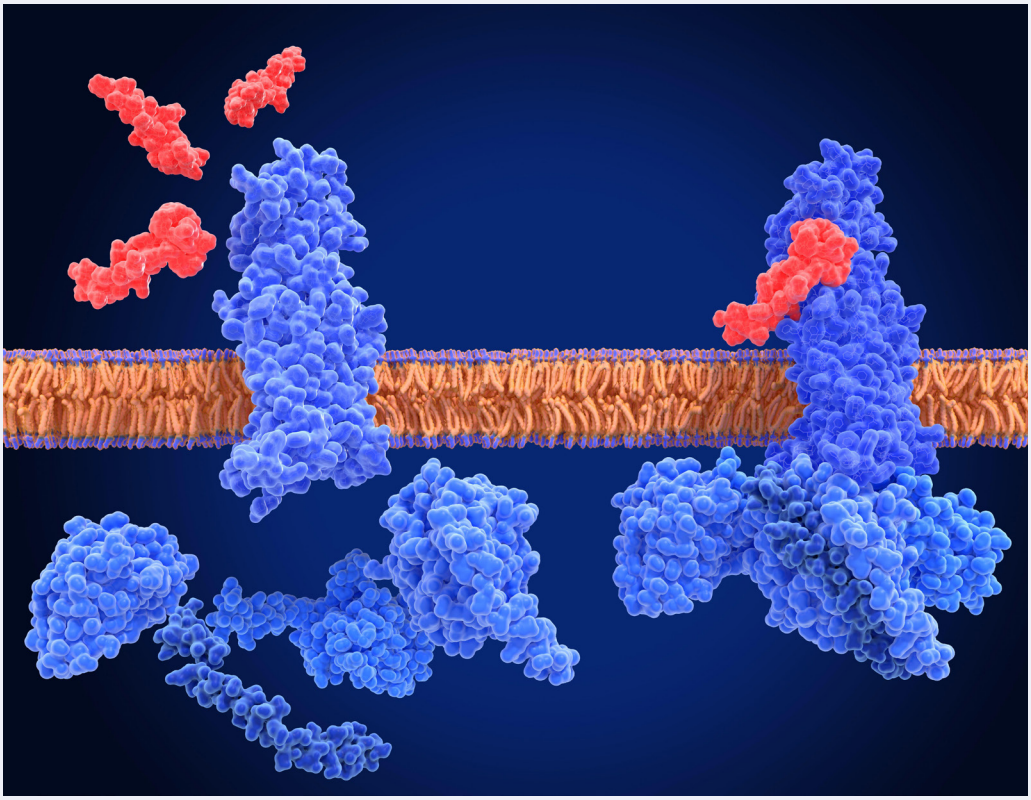
Methods In this study, the UK Clinical Practice Research Datalink linked to the Hospital Episodes Statistics and Death Registration databases was used to assemble two active comparator, new user cohorts of patients with type 2 diabetes starting treatment with either a GLP-1 receptor agonist or a DPP-4 inhibitor between 1 January 2007 and 31 December 2020 (cohort 1) or a GLP-1 receptor agonist or an SGLT-2 inhibitor between 1 January 2013 and 31 December 2020 (cohort 2), with follow-up until 29 March 2021. The two groups were compared using Cox proportional hazards models with propensity score fine stratification weighting accounting for 57 covariates to estimate the hazard ratio and 95% confidence interval (CI) for a composite of suicidal ideation, self-harm, or death from suicide.

Study answer and limitations Cohort 1 included 36 082 GLP-1 receptor agonist users and 234 028 DPP-4 inhibitor users; cohort 2 included 32 336 GLP-1 receptor agonist users and 96 212 SGLT-2 inhibitor users. In both cohorts, weighted models showed no association between GLP-1 receptor agonist use and the composite outcome when compared with either DPP-4 inhibitor users or SGLT-2 inhibitor users (hazard ratio 1.02 (95% CI 0.85 to 1.23) and

COMMENTARY Evidence suggests no increased risk

The use of glucagon-like peptide-1 (GLP-1) receptor agonists has surged in recent years, driven by their benefits in glucose control in type 2 diabetes, weight reduction, and cardiovascular and renal outcomes. Given the increasing number of patients being treated with these drugs, timely assessment of potential safety signals is important.

In July 2023, the European Medicines Agency launched an investigation into thoughts of suicide and self-harm potentially linked to GLP-1 receptor agonists.[1] Although meta-analyses of randomised controlled trials have not indicated that GLP-1 receptor agonists increase suicidality, depression, anxiety, and other adverse mental health outcomes, the clinical trials were not designed to assess those outcomes, and the statistical power of the analyses has been limited by the low number of events.[2 3] In addition, most clinical trials have excluded patients at high risk of suicidality. In this situation, adequately designed observational studies are warranted.



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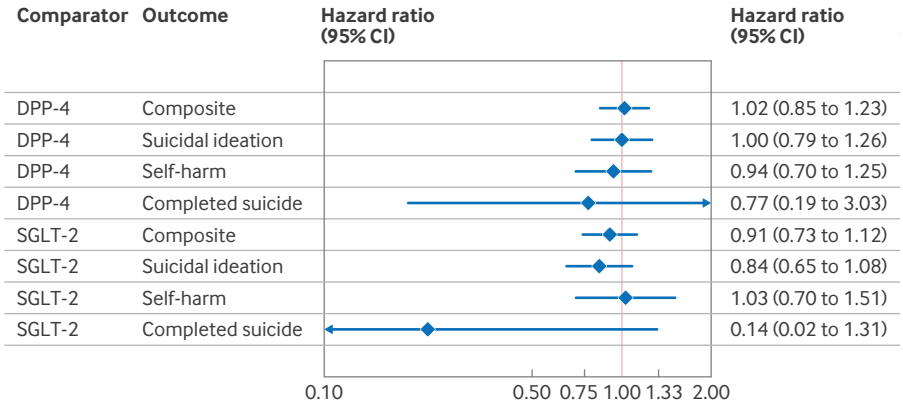
What did the authors find?

In the linked paper, Shapiro and colleagues report a cohort study of more than 30 000 users of GLP-1 receptor agonists with type 2 diabetes in the UK using data from the Clinical Practice Research Datalink (CPRD).[4] The primary study outcome was suicidality, a composite of suicidal ideation, self-harm, and death from suicide. In separate analyses using dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter-2 (SGLT-2) inhibitors as comparators, they found no indication of an increased risk associated with GLP-1 receptor agonists, with upper limits of

0.91 (0.73 to 1.12), respectively), with consistent results across secondary and sensitivity analyses. Residual confounding remains a possibility.

What this study adds GLP-1 receptor agonists do not seem to increase the risk of suicidal ideation, self-harm, or suicide among patients with type 2 diabetes.

Funding, competing interests, and data sharing This study was funded by a Foundation Scheme grant from the Canadian Institutes of Health Research. See full article on bmj.com for competing interests. No additional data available.



Hazard ratios and 95% confidence intervals (CIs) for composite outcome of suicidal ideation, self-harm, and suicide and each outcome individually among patients with type 2 diabetes taking a glucagon-like peptide-1 receptor agonist compared with taking a dipeptidyl peptidase-4 inhibitor (DPP-4) or a sodium-glucose cotransporter-2 inhibitor (SGLT-2)

the 95% confidence intervals for the hazard ratio at 1.23 (versus DPP-4 inhibitors) and 1.12 (versus SGLT-2 inhibitors). In this broad study population, event rates were low and the analyses ruled out moderate magnitudes of increases in risk on both the relative and the absolute scale.

In contrast to some of the previous analyses of data from routine clinical practice,[5] the study by Shapiro and colleagues used appropriate comparator drugs and an active comparator new user design, which is not affected by time related biases such as immortal time bias.[6] Their findings were largely consistent across several analyses using both comparator drugs. Although potentially small increased risks in the broader study populations are unlikely to affect treatment decisions, people at high risk of suicidality owing to previous or existing psychiatric conditions comprise a subgroup of specific interest.[7] The analyses by Shapiro and colleagues found no signs of a higher risk linked to GLP-1 receptor agonists in this subgroup.[4]

Outcome ascertainment

The study, however, has important limitations. Around two thirds of the composite outcome events comprised suicidal ideation. This outcome is inconsistently and incompletely captured in routinely collected databases.[8] The study does not describe the content and definition of this outcome that was recorded in the CPRD, and uncertainty remains about its completeness and validity, especially as the reliability of other related diagnoses is limited in this database.[9] The remaining third of the outcome events in the study mostly comprised self-harm events, which are also incompletely captured in databases from routine clinical practice.[10 11] Meanwhile, deaths from suicide, the most reliable and clinically relevant study outcome, could not be assessed in detail: in the GLP-1 receptor agonist group, only six events were captured in analyses versus DPP-4 inhibitors and fewer than five events in analyses versus SGLT-2 inhibitors, yielding imprecise and inconclusive

MOHAMMED AL/ALAMY

Most clinical trials have excluded patients at high risk of suicidality

estimates.[4] Moreover, the proportion of GLP-1 receptor agonist users who used drugs that are rarely prescribed in contemporary clinical practice (exenatide and lixisenatide) was around 40% in analyses versus DPP-4 inhibitors and 23% in analyses versus SGLT-2 inhibitors. Semaglutide, the most widely used GLP-1 receptor agonist today, was used by less than 10% of the patients who were treated with GLP-1 receptor agonists. Future studies may specifically assess the safety of semaglutide and tirzepatide, which have surpassed other GLP-1 receptor agonists in popularity owing to their larger effects on weight reduction and glucose control.

The carefully conducted and adequately designed study by Shapiro and colleagues adds to the existing literature on the safety of GLP-1 receptor agonists.[2-14] At this point in time, data from clinical trials and observational studies in broad populations do not indicate that GLP-1 receptor agonists increase the risk of suicidality.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.r351

ORIGINAL RESEARCH Open label, three arm, randomised, multicentre, phase 3 trial

Plain versus drug balloon and stenting in severe ischaemia of the leg (BASIL-3)

Bradbury AW, Hall JA, Popplewell MA, et al

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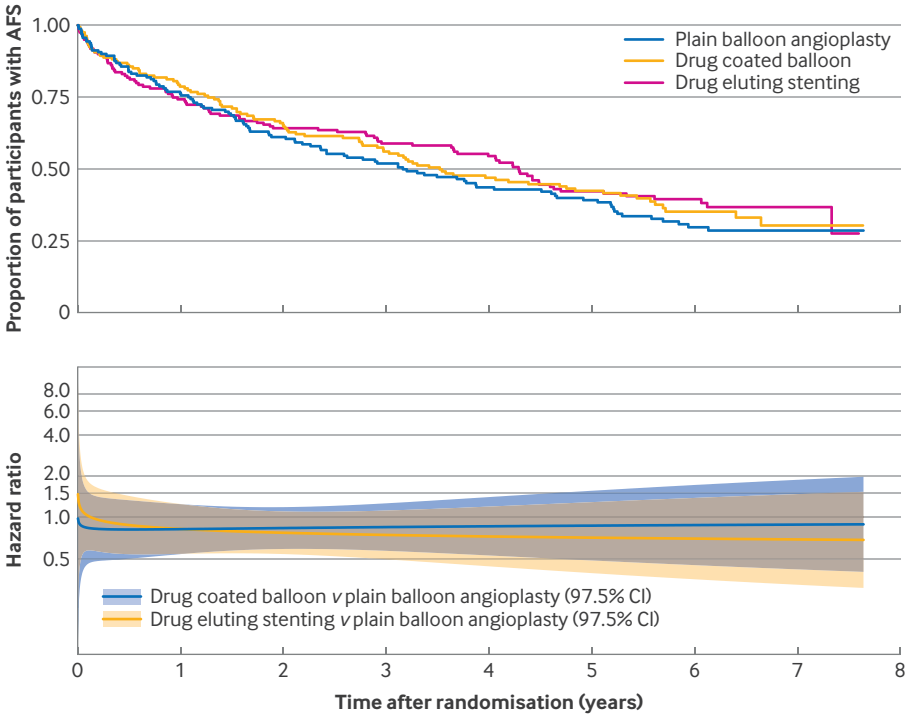
Find this at doi: 10.1136/bmj-2024-080881



Amputation-free survival (AFS) Kaplan-Meier plot and hazard ratio over time fitted assuming non-proportional hazards (intention-to-treat analysis). CI=confidence interval

Study question What is the most clinically effective, primary endovascular treatment for patients with chronic limb threatening ischaemia who require endovascular femoro-popliteal, with or without infra-popliteal, revascularisation?

Methods This three arm, open label, pragmatic, multicentre, randomised, phase 3 superiority trial was conducted in 35 UK NHS vascular units. Patients with chronic limb threatening ischaemia who required an endovascular procedure to restore perfusion were recruited. Participants were randomised in a 1:1:1 ratio to drug coated balloon angioplasty (DCBA) with or without bare metal stenting (BMS), primary drug eluting stenting (DES) (intervention arms), or plain balloon angioplasty (PBA) with or without BMS (control). The primary outcome was amputation free survival defined as time to first major amputation or death from any cause.

Study answer and limitations Between 29 January 2016 and 31 August 2021, 481 patients were randomised. Major amputation or death occurred in 106 of 160 (66%) patients in the PBA with or without BMS group, 97 of 161 (60%) in the DCBA with or without BMS group, and 93 of 159 (58%) in the DES group (adjusted hazard ratios: PBA with or without BMS *v* DCBA with or without BMS: 0.84, 97.5% confidence interval 0.61 to 1.16, P=0.22; PBA with or without BMS *v* DES: 0.83, 0.60 to 1.15, P=0.20). Smaller absolute differences in the primary outcome cannot be excluded, but it is unclear if any smaller absolute difference would be clinically meaningful.

What this study adds The use of drug coated balloons and drug eluting stents in the femoro-popliteal segment did not confer clinical benefit over the use of plain balloons and bare metal stents in patients with chronic limb threatening ischaemia undergoing endovascular revascularisation.

Funding, competing interests, and data sharing
BASIL-3 was funded by the National Institute for Health and Care Research, Health Technology Assessment. No competing interests declared. Participant level data available within 6 months of publication on reasonable request at discretion of corresponding author.

Trial registration ISRCTN14469736.

CORRECTION

Efficacy of psilocybin for treating symptoms of depression: systematic review and meta-analysis

This research paper by Metaxa and Clarke (*BMJ* 2024;385:e078084, doi:10.1136/bmj-2023-078084, published in print issue of 4 May 2024) has a correction notice. For more details please go to bmj.com.