



Combined associations of GLP-1 receptor agonists and a healthy lifestyle with cardiovascular outcomes among individuals with type 2 diabetes: a prospective cohort study

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Summary

Background The long-term combined effects of lifestyle habits and GLP-1 receptor agonists on cardiovascular outcomes are unknown. We aimed to examine the combined association of GLP-1 receptor agonist use and adherence to eight lifestyle habits with cardiovascular outcomes.

Methods We did a prospective cohort study of individuals with type 2 diabetes enrolled within the US Veterans Affairs' Million Veteran Program between Jan 10, 2011, and Sept 30, 2023. Participants had no previous history of myocardial infarction, stroke, or advanced chronic kidney disease. The eight low-risk lifestyle habits assessed were a higher quality diet, being physically active, not smoking, restful sleep, no heavy alcohol intake, good stress management, social connection and support, and no opioid use disorder. We assessed the risk of major adverse cardiovascular events (MACE), defined as non-fatal stroke or myocardial infarction, or cardiovascular death, according to GLP-1 receptor agonist use and low-risk lifestyle habits using Cox proportional hazard regression models.

Findings Of the 963 753 veterans enrolled, a total of 98 261 participants were included in the study with 632 543 person-years of follow-up, during which 10 443 people developed MACE. Multivariable-adjusted hazard ratio (HR) of MACE was 0.40 (95% CI 0.30–0.54) when comparing participants adhering to all eight low-risk lifestyle habits to those adopting one habit or less. Multivariable-adjusted HR of MACE was 0.84 (0.76–0.92) when comparing users of GLP-1 receptor agonists with non-users. Participants using GLP-1 receptor agonists and adhering to six to eight low-risk lifestyle factors had a 43% lower risk of MACE than did those with three or fewer low-risk lifestyle factors and no GLP-1 receptor agonist use (0.57; 0.46–0.71).

Interpretation Adherence to low-risk lifestyle habits combined with GLP-1 receptor agonist use was associated with a greater reduction in MACE risk than either approach alone, underscoring the importance of integrating lifestyle modification with pharmacotherapy in type 2 diabetes management.

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Introduction

In the USA, the number of individuals with diabetes has more than doubled in the past 20 years, with 29.1 million people, or 12.0% of the US population, living with diabetes in 2021.¹ With the increasing ageing population, the epidemiology of type 2 diabetes is shifting towards older age with increasing prevalence of comorbidities. Obesity is considered a major driver of long-term comorbidities among patients with type 2 diabetes, in particular cardiovascular disease.² Its management encompasses lifestyle modifications and pharmacological therapies, each offering varying degrees of success in weight loss and cardiovascular disease risk reduction.

GLP-1 receptor agonists, such as liraglutide and semaglutide, are a class of popular weight loss medications that mimic a naturally occurring hormone, GLP-1, in the body. They show benefit in not only

reducing bodyweight, but also improving blood sugar control in patients with type 2 diabetes.³ Additionally, some cardiovascular outcome trials have shown that GLP-1 receptor agonists have a cardioprotective effect and reduce the risk of major adverse cardiovascular events (MACE).^{4,6} Among patients with type 2 diabetes, GLP-1 receptor agonists significantly lowered incidence of MACE when compared with older antihyperglycemic drug classes⁴ and usual care,⁵ such as biguanides and sulfonylureas.

Despite advances in pharmacological therapies, lifestyle modification remains the cornerstone of type 2 diabetes management.⁷ To our knowledge, the long-term combined effect of a healthy lifestyle and GLP-1 receptor agonists on major adverse cardiovascular disease has not yet been fully studied. Our aim was to investigate the independent and combined association of a healthy lifestyle and GLP-1 receptor agonists on the risk of MACE

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Research in context

Evidence before this study

We searched PubMed for publications from database inception to May 28, 2025, using the terms “((lifestyle) OR (preventive medicine)) AND ((GLP-1) OR (liraglutide) OR (semaglutide) OR (dulaglutide)) AND (diabetes) AND ((stroke) OR (heart) OR (cardiovascular))” in all fields, with no language restrictions. We also reviewed references listed in the identified papers. Previous studies indicated that GLP-1 receptor agonists have a cardioprotective effect and reduce the risk of major adverse cardiovascular events (MACE) among patients with type 2 diabetes. Meta-analysis of 14 clinical trials indicated a 14% lower risk of MACE among GLP-1 RA users than for placebo (hazard ratio 0.86; 95% CI 0.80–0.93). Lifestyle modifications are recommended as the cornerstone for preventing and managing type 2 diabetes. However, comprehensive evaluations on the long-term combined effect of a healthy lifestyle and GLP-1 receptor agonists on MACE are scarce.

Added value of this study

With 632 543 person-years of follow-up among 98 261 US veterans with type 2 diabetes, we observed that although both a healthy lifestyle and GLP-1 receptor agonist use were independently associated with a low risk of MACE, a combination of GLP-1 receptor agonist use and a healthy lifestyle was associated with the lowest risk of MACE. To our knowledge, this is the first study to show that optimising nutrition and lifestyle can further mitigate cardiovascular risk in conjunction with pharmacotherapy in type 2 diabetes.

Implications of all the available evidence

These findings underscore the importance of integrating lifestyle modification with pharmacotherapy in reducing cardiovascular complications among individuals with type 2 diabetes.

For more on the **Million Veteran Program** see mvp.va.gov

among participants with type 2 diabetes in the Million Veteran Program (MVP).

Methods

Study design

MVP is a nationally representative, prospective cohort study of veterans in the USA designed to examine genetic and non-genetic determinants of chronic diseases. MVP combines data from self-reported surveys (MVP Baseline and Lifestyle Surveys), electronic health records (EHRs), and biospecimen samples collected at baseline. Details of the research design can be found elsewhere.⁸ Enrolment of MVP participants began on Jan 10, 2011, and we included participants up to Sept 30, 2023. All participants signed informed consent, and the Veteran Affairs Central Institutional Review Board approved the MVP protocol.

Participants

Participants were included if they completed the MVP Lifestyle Survey. Information collected from the MVP Baseline Survey and MVP Lifestyle Survey included data on age, sex, race, education, bodyweight, height, and lifestyle factors at baseline. Additional information on health conditions, comorbidities, and medication use was obtained through the Veterans Health Administration (VHA) EHR. We defined baseline for this research as the time a participant completed the MVP Lifestyle Survey and the end of follow-up as Sept 30, 2023, incident myocardial infarction, incident stroke, or death, whichever came first.

We excluded participants with implausible death records or withdrawal from MVP and participants with a diagnosis of myocardial infarction or stroke, or individuals with advanced chronic kidney disease (estimated glomerular filtration rate <30 mL/min per 1.73 m², dialysis, or kidney transplant) at or before

baseline. To minimise potential reverse causality, we further excluded participants with total follow-up time less than 1 year as of Sept 30, 2023, or less than 1 year after initiating GLP-1 RA therapy.

Procedures

We included eight low-risk lifestyle factors: healthy eating habits, being physically active, non-smoking, having restful sleep, no or moderate alcohol intake (ie, absence of frequent heavy drinking), good stress management, being socially connected and supported, and absence of opioid drug addiction, as described in detail previously.^{8,9}

In brief, healthy eating habits were assessed with the healthful plant-based diet index (hPDI).¹⁰ Physical activity was assessed with the metabolic equivalent (MET) value that was assigned based on the intensity of physical activities and frequency of leisure time activities.¹¹ Stress was assessed by the four-item patient health questionnaire (PDQ-4) for anxiety and depression,¹² which included two questions for Generalised Anxiety Disorder 2 (GAD-2) and two questions for Patient Health Questionnaire 2 score (PHQ-2). Sleep was estimated by hours of usual sleep each day. Social support was estimated with the Medical Outcomes Survey¹³ for Social Support and smoking status was determined with an algorithm developed for VHA EHRs. Heavy alcohol drinking was assessed based on self-reported largest number of alcoholic drinks in a typical month and opioid use was identified with the VHA EHR.¹⁴

Assigned scoring for low-risk lifestyle factors was developed with eight subscores; each factor scored as 1 (healthy) or 0 (unhealthy). The composite lifestyle score consisted of eight low-risk lifestyle factors ranging from 0 to 8. A composite lifestyle score of 8, therefore, corresponded to adoption of all eight low-risk lifestyle

factors and a score of 1 or less, for example, corresponded to adoption of any one low-risk lifestyle factor or none.

The following are the scoring methods for each individual lifestyle factor. For healthy eating habits, 1 was the upper 40% of hPDI; 0 was the lower 60% of hPDI. For being physically active, 1 was leisure time activity of 7.5 MET h/week or more; 0 was less than 7.5 MET h/week. For good stress management, 1 was GAD-2 lower than 3 and PHQ-2 lower than 3; 0 was GAD-2 of 3 or more or PHQ-2 of 3 or more. For restful sleep, 1 was sleep duration of 7–9 h/day; 0 was otherwise. For being socially connected and supported, 1 was a positive social interaction score of 50 or higher; 0 was a score below 50. For non-smoking, 1 was never smoker; 0 was ever smoker. For no frequent heavy alcohol intake, 1 was never drinking or typically no more than four drinks in a day for male participants or no more than three drinks for female participants (largest number of alcoholic drinks consumed in 1 day in a typical month); 0 was five or more drinks for men (four or more drinks for women) within 1 day in a typical month. For absence of opioid drug addiction, 1 was no opioid use; 0 was opioid use.

For participants with missing data on any of the eight lifestyle factors ($n=16\,976$; 85.4% missing one, 10.9% missing two, and 3.7% missing three to six factors), composite lifestyle score was calculated as the average score of available lifestyle subscores and then multiplied by 8 to retain all participants in the analytical population.¹⁵

We also derived an expanded composite lifestyle score by assigning weights to each composite lifestyle score based on the β -coefficients from the multivariable-adjusted Cox model with MACE as the outcome. We then summed the products of each binary composite lifestyle score multiplied by its weight, divided it by the sum of all β -coefficient values, and then multiplied by 8 and rounded it to the nearest whole number to make the expanded composite lifestyle score easier to interpret. In this way, the expanded composite lifestyle score ranged from 0 to 8, and each unit of the composite lifestyle score represented the change in one individual risk factor.

All GLP-1 receptor agonists that were approved for use in the USA were identified in the VHA pharmacy database by either the generic or trade name of each medication (appendix p 5). For each prescription, the pharmacy records provided the prescription date and days of supply. In the main analysis, GLP-1 receptor agonist users were classified as ever users. Pre-enrolment users were defined as patients who initiated GLP-1 receptor agonist therapy either at or before MVP enrolment. Post-enrolment users were those who initiated GLP-1 receptor agonist therapy during follow-up, after baseline enrolment. Total supply time was calculated as the cumulative number of days for which the GLP-1 receptor agonists were dispensed to each participant.

To assess the consistency of GLP-1 receptor agonist use, the data were sorted by prescription date, and the gaps between consecutive fills were evaluated. If the gap between the end of one prescription's supply and the start of the next prescription was within 90 days (including any overlaps), the prescriptions were considered part of continuous use. If the gap exceeded 90 days, the subsequent prescription was treated as the start of a new use period. This process was repeated until the end of follow-up.

Outcomes

MACE, including a non-fatal stroke (either ischaemic or haemorrhagic), non-fatal myocardial infarction, or cardiovascular death, were identified through combined information from the VA Corporate Data Warehouse,^{16,17} which is the VA equivalent of an EHR system and National Death Index database by use of the ICD-9 and ICD-10 codes. Veterans were classified as having MACE if they had one diagnosis or more as an inpatient or two diagnoses or more as an outpatient within the follow-up period.

Information on covariates, including age, BMI, race, family income, current marital status, and education level, was collected through self-reported surveys at baseline. Diagnosis of comorbidities and use of medications were derived from Corporate Data Warehouse data.¹⁸

Statistical analysis

We calculated person-years from the date of return of the lifestyle questionnaire to the date of diagnosis of myocardial infarction, stroke, death, or the end of the follow-up (Sept 30, 2023), whichever came first. We applied Cox proportional hazard regression models to estimate hazard ratios (HRs) and 95% CIs for MACE, comparing composite lifestyle scores of 2–8 with a score of 0 or 1, and use of GLP-1 receptor agonists versus non-GLP-1 receptor agonist or usual care, as well as their joint classification groups. To account for left truncation and time-varying covariates, a counting process data structure was used, and the Cox proportional hazard models were jointly stratified on age (in months) and calendar year. Age in years was used as the time scale in the analysis, based on the data structure and the formulation of the analytic model. The composite lifestyle score was assessed at the time of enrolment only and carried forward during follow-up. GLP-1 receptor agonist prescriptions and supply durations were repeatedly collected and treated as time-varying variables during follow-up: once prescribed, either at baseline or during follow-up, the exposure was carried forward according to the intention-to-treat approach. Covariates included both baseline and time-updated variables. Baseline covariates were measured at time of enrolment for the entire population and redefined at the time of new GLP-1 receptor agonist use for those who started GLP-1 receptor agonists during the follow-up. The sex, race, ethnicity,

See Online for appendix

family income, current marital status, education level, and family history of heart disease covariates were collected only once and carried forward during follow-up. BMI; diagnosis of hypertension, dyslipidaemia, atrial fibrillation, or cancer; use of statins, other lipid-lowering medications, antihypertensive medications, metformin, sulfonylureas, insulin, DPP4 inhibitor, SGLT2 inhibitor, and GLP-1 receptor agonist status were assessed annually and treated as time-varying covariates. Once a diagnosis was made or a medication was prescribed, that status was carried forward in subsequent years, except for BMI, which was updated annually.

To estimate the potential additive or synergistic effect between GLP-1 receptor agonists and healthy lifestyle, we classified participants according to the joint categories of GLP-1 receptor agonist use (vs non-GLP1 receptor agonist use or usual care) and the categories of composite lifestyle score (0–3 for unhealthy, 4–5 for intermediate, and 6–8 for healthy lifestyle). We tested the multiplicative interaction by comparing the –2 log-likelihood of the

multivariate adjusted models with and without the cross-product interaction terms.¹⁹ To assess the additive interaction between patients not using GLP-1 receptor agonists and unhealthy lifestyle, we considered the inverse number of composite lifestyle score as a continuous variable and assessed the relative excess risk due to interaction as a metric of additive interaction.¹⁹

To test the robustness of our estimation of GLP-1 receptor agonist effectiveness, we did several sensitivity analyses. First, we did a per-protocol analysis of maintained use of GLP-1 receptor agonists. Participants were considered to have discontinued the use of GLP-1 receptor agonists if they did not receive a refill by 90 days after the end of supply. Then we updated the continued use of GLP-1 receptor agonists in the time-varying models, in which discontinued use of GLP-1 receptor agonists was coded as non-users of GLP-1 during the follow-up after the discontinuation. Second, we excluded participants with a total supply of GLP-1 receptor agonists for no more than 12 weeks and conducted analyses only

	0 or 1	2	3	4	5	6	7	8
Participants (n=98 261)	2265 (2.3%)	7645 (7.8%)	16 062 (16.3%)	25 475 (25.9%)	26 366 (26.8%)	15 206 (15.5%)	4320 (4.4%)	922 (0.9%)
Mean age, years (SD)	62.8 (8.5)	64.5 (9.2)	66.3 (9.3)	68.3 (9.2)	69.3 (9.4)	69.8 (9.2)	69.2 (9.1)	68.9 (9.2)
Sex								
Female	121 (5.3%)	471 (6.2%)	905 (5.6%)	1282 (5.0%)	1470 (5.6%)	838 (5.5%)	276 (6.4%)	63 (6.8%)
Male	2144 (94.7%)	7174 (93.8%)	15 157 (94.4%)	24 193 (95.0%)	24 896 (94.4%)	14 368 (94.5%)	4044 (93.6%)	859 (93.2%)
Mean BMI, kg/m ² (SD)	32.5 (6.7)	32.5 (6.5)	32.2 (6.3)	31.8 (6.1)	31.4 (5.8)	30.7 (5.5)	30.2 (5.4)	29.6 (5.4)
Mean duration of type 2 diabetes, years (SD)	7.0 (5.0)	7.1 (5.1)	7.0 (5.0)	7.1 (5.0)	7.0 (5.0)	6.9 (5.0)	6.5 (4.9)	6.6 (5.0)
Race*								
White	1616 (72.1%)	5637 (74.3%)	12 290 (77.4%)	20 440 (80.9%)	21 950 (83.9%)	12 906 (85.5%)	3723 (86.9%)	785 (86.0%)
Black	497 (22.2%)	1530 (20.2%)	2796 (17.6%)	3746 (14.8%)	3227 (12.3%)	1676 (11.1%)	426 (9.9%)	88 (9.6%)
Other races	127 (5.7%)	425 (5.6%)	799 (5.0%)	1084 (4.3%)	983 (3.8%)	513 (3.4%)	136 (3.2%)	40 (4.4%)
Hispanic	250 (11.0%)	731 (9.6%)	1454 (9.1%)	1944 (7.6%)	1816 (6.9%)	1034 (6.8%)	286 (6.6%)	75 (8.1%)
Non-Hispanic	2015 (89.0%)	6914 (90.4%)	14 608 (90.9%)	23 531 (92.4%)	24 550 (93.1%)	14 172 (93.2%)	4034 (93.4%)	847 (91.9%)
Marriage status*								
Currently married	1818 (40.6%)	6284 (47.9%)	13 392 (55.4%)	21 483 (62.2%)	22 700 (68.3%)	13 321 (73.0%)	3839 (75.4%)	771 (75.0%)
Not married	1080 (59.4%)	3277 (52.1%)	5976 (44.6%)	8129 (37.8%)	7185 (31.7%)	3593 (27.0%)	943 (24.6%)	193 (25.0%)
Educational level*								
High school	633 (34.7%)	2095 (33.1%)	4269 (31.7%)	6517 (30.1%)	5911 (25.8%)	2661 (19.8%)	556 (14.4%)	79 (10.2%)
Some college	676 (37.1%)	2260 (35.7%)	4621 (34.3%)	7030 (32.5%)	7232 (31.6%)	3920 (29.2%)	971 (25.1%)	175 (22.6%)
College or higher	513 (28.2%)	1968 (31.1%)	4571 (34.0%)	8091 (37.4%)	9728 (42.5%)	6834 (50.9%)	2343 (60.5%)	519 (67.1%)

(Table 1 continues on next page)

	0 or 1	2	3	4	5	6	7	8
(Continued from previous page)								
Family annual income	1705	5824	12 261	19 549	20 624	12 000	3479	686
<US\$30 000	901 (52.8%)	2712 (46.6%)	5079 (41.4%)	7054 (36.1%)	6309 (30.6%)	3004 (25.0%)	716 (20.6%)	130 (19.0%)
\$30 000–\$60 000	581 (34.1%)	2107 (36.2%)	4542 (37.0%)	7488 (38.3%)	8111 (39.3%)	4677 (39.0%)	1257 (36.1%)	235 (34.3%)
>\$60 000	223 (13.1%)	1005 (17.3%)	2640 (21.5%)	5007 (25.6%)	6204 (30.1%)	4319 (36.0%)	1506 (43.3%)	321 (46.8%)
Family history of heart diseases	683 (30.2%)	2385 (31.2%)	5159 (32.1%)	8681 (34.1%)	9497 (36.0%)	5757 (37.9%)	1757 (40.7%)	351 (38.1%)
Smoking status	2244	7545	15 755	24 879	25 547	14 656	4135	881
Current	990 (44.1%)	2495 (33.1%)	4043 (25.7%)	4715 (19.0%)	3389 (13.3%)	1157 (7.9%)	151 (3.7%)	0.0
Ever	1241 (55.3%)	4474 (59.3%)	9677 (61.4%)	15 291 (61.5%)	14 357 (56.2%)	6347 (43.3%)	1087 (26.3%)	0.0
Never	13 (0.6%)	576 (7.6%)	2035 (12.9%)	4873 (19.6%)	7801 (30.5%)	7152 (48.8%)	2897 (70.1%)	881 (100%)
No frequent heavy alcohol drinking*	90/1950 (4.6%)	1757/6552 (26.8%)	6091/14 399 (42.3%)	12 953/22 476 (57.6%)	18 246/23 678 (77.1%)	12 676/14 074 (90.1%)	4171/4320 (96.6%)	712/712 (100%)
Upper healthy Plant Diet Index score*	52/1933 (2.7%)	939/6745 (13.9%)	3340/14 888 (22.4%)	7332/23 444 (31.3%)	11 375/24 856 (45.8%)	9803/14 622 (67.0%)	3681/4320 (85.2%)	829/829 (100%)
Physically active ≥ 7.5 MET h/week*	15/2252 (0.7%)	214/7586 (2.8%)	863/15 980 (5.4%)	2218/25 227 (8.8%)	3903/26 218 (14.9%)	4524/15 111 (29.9%)	2573/4320 (59.6%)	869/869 (100%)
Sleep 7–9 h/day*	50/2207 (2.3%)	1026/7456 (13.8%)	4821/15 990 (30.2%)	13 005/25 184 (51.6%)	18 817/26 189 (71.9%)	12 966/15 131 (85.7%)	4021/4320 (93.1%)	883/883 (100%)
No opioid use disorder	1698 (75.0%)	7030 (92.0%)	15 537 (96.7%)	25 182 (98.8%)	26 261 (99.6%)	15 184 (99.9%)	4319 (100%)	922 (100%)
Neither anxiety nor depression*	70/2119 (3.3%)	1872/7157 (26.2%)	8523/15 559 (54.8%)	19 279/24 529 (78.7%)	23 550/25 876 (91.0%)	14 548/15 010 (96.9%)	4274/4320 (98.9%)	868/868 (100%)
Positive social interaction score ≥ 50 *	119/2145 (5.5%)	1740/7319 (23.8%)	6818/15 743 (43.3%)	15 759/24 796 (63.6%)	20 767/25 897 (80.2%)	13 609/15 009 (90.7%)	4167/4320 (96.5%)	868/868 (100%)
Baseline disease status								
Dyslipidaemia	1896 (83.7%)	6480 (84.8%)	13 671 (85.1%)	21 883 (85.9%)	22 591 (85.7%)	12 920 (85.0%)	3645 (84.4%)	769 (83.4%)
Hypertension	2040 (90.1%)	6912 (90.4%)	14 447 (89.9%)	22 954 (90.1%)	23 452 (88.9%)	13 334 (87.7%)	3681 (85.2%)	774 (83.9%)
Atrial fibrillation	217 (9.6%)	778 (10.2%)	1771 (11.0%)	2941 (11.5%)	3047 (11.6%)	1673 (11.0%)	408 (9.4%)	75 (8.1%)
Cancer	396 (17.5%)	1406 (18.4%)	3138 (19.5%)	5280 (20.7%)	5351 (20.3%)	2916 (19.2%)	787 (18.2%)	174 (18.9%)
Use of medications at baseline								
Statins	1853 (81.8%)	6264 (81.9%)	13 157 (81.9%)	20 633 (81.0%)	20 800 (78.9%)	11 726 (77.1%)	3226 (74.7%)	681 (73.9%)
GLP-1 receptor agonists	61 (2.7%)	245 (3.2%)	509 (3.2%)	791 (3.1%)	755 (2.9%)	376 (2.5%)	104 (2.4%)	21 (2.3%)
Metformin	1608 (71.0%)	5437 (71.1%)	11 104 (69.1%)	17 078 (67.0%)	17 171 (65.1%)	9586 (63.0%)	2621 (60.7%)	522 (56.6%)
Sulfonylureas	1002 (44.2%)	3513 (46.0%)	7097 (44.2%)	10 990 (43.1%)	10 790 (40.9%)	5933 (39.0%)	1556 (36.0%)	319 (34.6%)
DPP4 inhibitors	57 (2.5%)	231 (3.0%)	521 (3.2%)	825 (3.2%)	877 (3.3%)	438 (2.9%)	130 (3.0%)	24 (2.6%)
SGLT2 inhibitors	49 (2.2%)	195 (2.6%)	405 (2.5%)	688 (2.7%)	646 (2.5%)	324 (2.1%)	99 (2.3%)	12 (1.3%)
Insulin	793 (35.0%)	2530 (33.1%)	5064 (31.5%)	7600 (29.8%)	7497 (28.4%)	3994 (26.3%)	1054 (24.4%)	205 (22.2%)

Data are n (%), N, or n/N (%), unless otherwise stated. *Numbers of participants with missing data are: 821 for race, 14 653 for marriage status, 14 088 for education, 22 133 for income, 2619 for smoking status, 10 100 for drinking alcohol, 6624 for diet score, 698 for physical activity, 901 for sleep, 2813 for anxiety or depression, and 2164 for social interaction.

Table 1: Baseline characteristics according to composite lifestyle score

among GLP-1 receptor agonist users with a total supply duration of more than 12 weeks. Third, to address confounding by indication, or factors influencing whether GLP-1 receptor agonist medications were prescribed, we developed a propensity score as the estimated probability of GLP-1 receptor agonist use conditional on observed covariates, using a logistic regression within each calendar year. We then applied the propensity score stratification method and propensity score overlap weighting method²⁰ in the sensitivity analyses to estimate

the main effect of GLP-1 receptor agonists use versus non-GLP-1 receptor agonist or usual care. Finally, we further excluded MVP participants with a diagnosis of cancer at or before baseline or those with missing data in any of the eight low-risk lifestyle factors, then repeated the main analysis among these participants.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

963753 veterans were enrolled in the study, and after exclusion, the analytical population included 98261 participants (5426 women and 92835 men) with type 2 diabetes (appendix p 2) Participants with a higher composite lifestyle score were more likely to be currently married, were more likely to have a higher level of education and family income, were less likely to have obesity, and were less likely to be Black (table 1).

Over a total of 632543 person-years of follow-up, 10443 participants with type 2 diabetes developed MACE (3937 myocardial infarctions, 903 strokes, 5938 cardiovascular deaths; table 2, appendix pp 3, 6). The incidence rate of MACE showed a graded inverse association with the number of adopted low-risk lifestyle factors, ranging from 199 per 10000 person-years among those with none or only one low-risk lifestyle factor to 88 per 10000 person-years among those with all eight (table 2). After adjustment for age, sex, duration of type 2 diabetes, BMI, race, ethnicity, education, income, marital status, family history of heart disease, diagnosis of dyslipidaemia, hypertension, cancer and atrial fibrillation at or before baseline; ever use of statin, other lipid-lowering medications, antihypertensive medications, GLP-1 receptor agonists, metformin, sulfonylureas, insulin, DPP4 inhibitor, or SGLT2 inhibitor at or before baseline; and individual low-risk lifestyle mutually adjusted. HR2=HR from model 2: same covariates as HR1 but applying time-varying updated status during follow-up for BMI, diagnosis of dyslipidaemia, hypertension, cancer, and atrial fibrillation; use of statin, other lipid-lowering medications, antihypertensive medications, GLP-1 receptor agonists, metformin, sulfonylureas, insulin, DPP4 inhibitors, and SGLT2 inhibitors.

The incidence rate of MACE showed a graded inverse association with the number of adopted low-risk lifestyle factors, ranging from 199 per 10000 person-years among those with none or only one low-risk lifestyle factor to 88 per 10000 person-years among those with all eight (table 2). After adjustment for age, sex, duration of type 2 diabetes, BMI, race, ethnicity, education, income, marital status, family history of heart disease, diagnosis of dyslipidaemia, hypertension, cancer and atrial fibrillation, and use of medications, the multivariable-adjusted HR of MACE was 0.40 (95% CI 0.30–0.54) when comparing participants with a composite lifestyle score of 8 with those with a score of 0 or 1. Further adjustment for quintiles of the predicted probabilities (propensity scores) for each level of the composite lifestyle score, estimated from the covariates in model 2, did not change the results. When examined individually, all eight low-risk lifestyle factors were significantly and independently associated with a lower risk of MACE among participants with type 2 diabetes (table 3). The associations were broadly consistent for myocardial infarction, stroke, and cardiovascular disease death (appendix p 6) and did not materially change in sensitivity analyses (appendix p 7).

Of the 98261 participants with type 2 diabetes, 13394 reported ever use of GLP-1 receptor agonists, whereas 84867 did not use GLP-1 receptor agonists (usual care). 2862 veterans (21.4% of all users) were pre-enrolment users and 10532 veterans (78.6% of all users) were post-enrolment users. 3752 (28%) had at least one gap of more than 90 days before being prescribed a GLP-1 receptor agonist. Among the 13394 users, 5.5%

	Participants, N	Person-years of follow-up	Cases, n	Incident rate (per 10 000 person years)	HR1 (95% CI)	HR2 (95% CI)
0 or 1	2265	14 639	292	199	1 (ref)	1 (ref)
2	7645	49 085	858	175	0.83 (0.73–0.95)	0.85 (0.75–0.98)
3	16 062	101 666	1828	180	0.78 (0.69–0.88)	0.80 (0.70–0.90)
4	25 475	161 279	2854	177	0.71 (0.63–0.80)	0.73 (0.64–0.82)
5	26 366	169 632	2775	164	0.63 (0.56–0.71)	0.65 (0.57–0.73)
6	15 206	100 416	1451	144	0.56 (0.49–0.64)	0.58 (0.51–0.66)
7	4320	29 333	328	112	0.50 (0.42–0.58)	0.50 (0.43–0.59)
8	922	6493	57	88	0.39 (0.29–0.52)	0.40 (0.30–0.54)
p value	<0.0001	<0.0001

HR=hazard ratio. HR1=HR from model 1: adjusted for age (continuous); sex; baseline BMI (continuous); duration of type 2 diabetes (continuous); race (White, Black, African American, or other); ethnicity (Hispanic, non-Hispanic); marital status (currently married, not married, or missing); educational level (high school or less, some years of college, college or higher, or missing); family income level (<US\$30 000, \$30 000–\$60 000, >\$60 000, or missing); family history of heart disease; ever diagnosis of dyslipidaemia, hypertension, cancer, and atrial fibrillation at or before baseline; ever use of statin, other lipid-lowering medications, antihypertensive medications, GLP-1 receptor agonists, metformin, sulfonylureas, insulin, DPP4 inhibitor, or SGLT2 inhibitor at or before baseline; and individual low-risk lifestyle mutually adjusted. HR2=HR from model 2: same covariates as HR1 but applying time-varying updated status during follow-up for BMI, diagnosis of dyslipidaemia, hypertension, cancer, and atrial fibrillation; use of statin, other lipid-lowering medications, antihypertensive medications, GLP-1 receptor agonists, metformin, sulfonylureas, insulin, DPP4 inhibitors, and SGLT2 inhibitors.

Table 2: HRs for major adverse cardiovascular events according to composite lifestyle score

	Cases, n/N (%)	HR1 (95% CI)	HR2 (95% CI)
Upper 40% of healthy Plant Diet Index (ie, a healthy diet)	37351/91637 (40.8%)	0.91 (0.87–0.95)	0.90 (0.86–0.94)
Physical activity ≥7.5 METs h/week	15179/97563 (15.6%)	0.81 (0.76–0.87)	0.80 (0.75–0.86)
Non-smoking	26228/95642 (27.4%)	0.82 (0.78–0.87)	0.82 (0.78–0.87)
No frequent heavy alcohol intake	56696/88161 (64.3%)	0.93 (0.89–0.97)	0.94 (0.89–0.98)
Sleeping 7–9 h/day	55589/97360 (57.1%)	0.93 (0.89–0.97)	0.93 (0.88–0.97)
No opioid use disorder	96133/98261 (97.8%)	0.73 (0.63–0.84)	0.77 (0.66–0.89)
Good stress management	73002/95448 (76.5%)	0.89 (0.84–0.95)	0.90 (0.85–0.95)
Positive social interaction score ≥50	63847/96097 (66.4%)	0.92 (0.88–0.97)	0.92 (0.88–0.97)

HR=hazard ratio. HR1=HR from model 1: adjusted for age (continuous); sex; baseline BMI (continuous); duration of type 2 diabetes (continuous); race (White, Black, African American, or other); ethnicity (Hispanic, non-Hispanic); marital status (currently married, not married, or missing); educational level (high school or less, some years of college, college or higher, or missing); family income level (<US\$30 000, \$30 000–\$60 000, >\$60 000, or missing); family history of heart disease; ever diagnosis of dyslipidaemia, hypertension, cancer, and atrial fibrillation at or before baseline; ever use of statin, other lipid-lowering medications, antihypertensive medications, GLP-1 receptor agonists, metformin, sulfonylureas, insulin, DPP4 inhibitor, or SGLT2 inhibitor at or before baseline; and individual low-risk lifestyle mutually adjusted. HR2=HR from model 2: same covariates as HR1 but applying time-varying updated status during follow-up for BMI, diagnosis of dyslipidaemia, hypertension, cancer, and atrial fibrillation; and use of statin, other lipid-lowering medications, antihypertensive medications, GLP-1 receptor agonists, metformin, sulfonylureas, insulin, DPP4 inhibitors, and SGLT2 inhibitors.

Table 3: HRs for major adverse cardiovascular events according to individual low-risk lifestyle factors

	Usual care (N=84 867)*	GLP-1 receptor agonists (N=13 394)†
Cases, n	9853	590
Person-years	591 412	41 130
Crude incident rate (per 10 000 person-years)	167	143
HR (95% CI)		
HR1	1 (ref)	0.74 (0.64–0.86)
HR2	1 (ref)	0.84 (0.76–0.91)
HR3	1 (ref)	0.84 (0.76–0.92)
MACE subtypes (HR3)		
Myocardial infarction	1 (ref)	0.88 (0.77–1.00)
Stroke	1 (ref)	0.75 (0.53–1.05)
Cardiovascular death	1 (ref)	0.79 (0.69–0.90)

The HRs were calculated with a Cox proportional hazards regression model. MACE=major adverse cardiovascular events. HR=hazard ratio. HR1=HR from model 1: adjusted for age (continuous), sex; baseline BMI (continuous); duration of type 2 diabetes (continuous); race (White, Black, African American, or other); ethnicity (Hispanic, non-Hispanic); marital status (currently married, not married, or missing); educational level (high school or less, some years of college, college or higher, or missing); family income level (<US\$30 000, \$30 000–\$60 000, >\$60 000, or missing); family history of heart disease; ever diagnosis of dyslipidaemia, hypertension, cancer, and atrial fibrillation at or before baseline; and ever use of statin, other lipid-lowering medications, antihypertensive medications, metformin, sulfonylureas, insulin, DPP4 inhibitors, or SGLT2 inhibitors at or before baseline. For those who were prescribed a GLP-1 receptor agonist after the baseline date, a second index baseline date was defined as the date of first GLP-1 receptor agonist prescription identified in Veterans Health Administration data, and baseline comorbidities and medication use were redefined based on this second baseline date. HR2=HR from model 2: same covariates as HR1 but applying time-varying updated status during follow-up for BMI; diagnosis of dyslipidaemia, hypertension, cancer, and atrial fibrillation; and use of statin, other lipid-lowering medications, antihypertensive medications, GLP-1 receptor agonists, metformin, sulfonylureas, insulin, DPP4 inhibitors, or SGLT2 inhibitors. HR3=HR from model 3: further adjusted for composite lifestyle score. *Individuals with type 2 diabetes and used non-GLP-1 receptor agonist anti-diabetes medications. †Initiated GLP-1 receptor agonists before baseline or during follow-up. Participants with type 2 diabetes who did not start GLP-1 receptor agonists at or before baseline were classified in the usual care group until they started a GLP-1 receptor agonist. This time-varying strategy allowed switching from the usual care group to the GLP-1 receptor agonists group once and then an intention-to-treat strategy was applied (ie, treated as GLP-1 receptor agonist during follow-up thereafter).

Table 4: Association between GLP-1 receptor agonist use and MACE compared with usual care among participants with type 2 diabetes

(n=738) had a total supply time of less than 12 weeks; 16.8% (n=2253) between 12 weeks to less than 1 year; 32.9% (n=4403) between 1 year and less than 2.5 years; 20.9% (n=2801) between 2.5 years and 4 years; and 23.9% (n=3199) for 4 years or longer. Users of GLP-1 receptor agonists had a higher baseline BMI, longer duration of type 2 diabetes, and greater proportion of ever use of other diabetes medications than did non-GLP-1 receptor agonist users or those who received usual care (appendix p 8). During the follow-up period, 590 cases of MACE were recorded among GLP-1 receptor agonist users and 9853 cases among non-GLP-1 receptor agonist or usual care participants, with crude incident rates of 143 per 10 000 person-years among GLP-1 receptor agonist users and 167 per 10 000 person-years for participants who received usual care. The

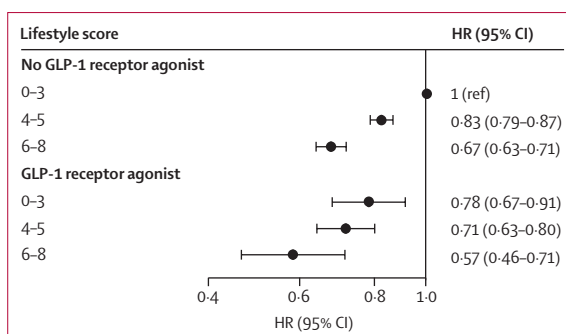


Figure 1: Joint associations between composite lifestyle score, use of GLP-1 receptor agonists, and major adverse cardiovascular events among participants with type 2 diabetes

HR=hazard ratio. Adjusted for age (continuous); sex; baseline BMI (continuous); duration of type 2 diabetes (continuous); race (White, Black, African American, or other); ethnicity (Hispanic, non-Hispanic); marital status (currently married, not married, or missing); educational level (high school or less, some years of college, college or higher, or missing); family income level (<US\$30 000, \$30 000–\$60 000, >\$60 000, or missing); family history of heart disease; ever diagnosis of dyslipidaemia, hypertension, cancer, and atrial fibrillation at or before baseline; and ever use of statin, other lipid-lowering medications, antihypertensive medications, metformin, sulfonylureas, insulin, DPP4 inhibitors, or SGLT2 inhibitors at or before baseline.

multivariable-adjusted HR of MACE was 0.74 (95% CI 0.64–0.86) when comparing GLP-1 receptor agonists use with usual care, which was attenuated to 0.84 (0.76–0.92) after adjustment for updated covariates during follow-up and further adjustment of lifestyle factors (table 4). The findings were broadly consistent for myocardial infarction, stroke, and cardiovascular disease deaths (table 4). The associations did not materially differ in sensitivity analyses after excluding GLP-1 receptor agonist users with a total medication supply time of less than 12 weeks in the main intention-to-treat analysis (0.81; 0.74–0.89) or among continuous users (0.76; 0.68–0.84; appendix p 9). Associations were strengthened after excluding participants diagnosed with MACE within the first 2 years of follow-up (0.63; 0.56–0.70). Results remained similar after applying the propensity score stratification adjustment (0.78; 0.71–0.85) or applying the propensity score overlap weighting method (0.77; 0.70–0.84) of MACE for GLP-1 receptor agonist use versus usual care, and between GLP-1 receptor agonist users initiated at or before baseline (0.76; 0.63–0.93) and during follow-up (0.83; 0.74–0.94; appendix p 9).

Both the use of GLP-1 receptor agonists and a healthy lifestyle (ie, adoption of six to eight healthy lifestyle factors) were independently associated with a lower risk of MACE without evidence of significant interactions ($p=0.6$ for multiplicative interaction and $p=0.08$ for additive interaction; figure 1). Compared with non-GLP-1 receptor agonist users who adopted three or fewer healthy lifestyle factors, the multivariable-adjusted HR of MACE was 0.78 (95% CI 0.67–0.91) among those who used GLP-1 receptor agonists with three or fewer healthy lifestyle factors, 0.67 (0.63–0.71) among non-GLP-1 receptor agonist users with six to eight adopted healthy

lifestyle factors, and 0.57 (0.46–0.71) among GLP-1 receptor agonist users who also adopted six to eight healthy lifestyle factors (figure 1). Individual low-risk lifestyle factors and GLP-1 receptor agonist use were both associated with lower risk of MACE, independent of each other, without evidence of significant interactions (interaction between use of GLP-1 receptor agonists and individual lifestyle factors $p > 0.05$; table 5). The results were consistent among subgroup populations (figure 2), and on individual MACE events (appendix p 3). Sensitivity analyses among 63 656 participants after excluding participants with missing lifestyle factors or a cancer diagnosis before or at baseline did not appreciably alter the findings (appendix pp 4, 10–12). Among the subgroup of the study population with biomarker data, GLP-1 receptor agonist users had greater improvement in glycaemic control and BMI, and slower age-related

worsening of cardiovascular risk assessed by the Pooled Cohort Equations than did non-users (appendix pp 13–14).

Discussion

With 632 543 person-years of follow-up among 98 261 US veterans with type 2 diabetes in this prospective cohort study, we observed that both a healthy lifestyle and GLP-1 receptor agonist use were independently associated with a low risk of MACE. The combination of adherence to a healthy lifestyle (ie, adoption of six to eight low-risk lifestyle factors) and GLP-1 receptor agonist use was associated with a 43% lower risk of MACE than for individuals with a less healthy lifestyle (three or fewer low-risk lifestyle factors) receiving usual care without GLP-1 receptor agonists.

Lifestyle modifications are recommended as the cornerstone for preventing and managing type 2 diabetes.^{7,9} Adopting positive health behaviours and maintaining psychological wellbeing are also important for reaching diabetes management goals and improving overall quality of life.²¹ A strength of our study was the availability of detailed data on GLP-1 receptor agonists and other medication use from the comprehensive VHA EHR, alongside information on diet and lifestyle factors, including never smoking, physical activity, no excessive alcohol consumption, restorative sleep, nutrition, stress management, social connections, and no opioid use disorder.⁹ Each low-risk lifestyle factor was associated with a low risk of MACE and the combination of all eight lifestyle factors together showed a continuous, graded inverse association. Our estimates of the association between lifestyle factors and MACE were consistent with other findings, although previous studies did not evaluate all eight low-risk factors collectively.^{8,22,23} Greater adherence to an overall healthy lifestyle, defined by consuming a higher-quality diet, not smoking, engaging in moderate to vigorous physical activity, and drinking alcohol in moderation, was associated with a substantially lower risk of cardiovascular disease incidence and mortality among individuals with type 2 diabetes in

two large prospective cohort studies of US health professionals.²² Previous analyses of the MVP or the UK Biobank cohort also found that adherence to these low-risk lifestyle factors was associated with increased longevity.^{8,24}

GLP-1 receptor agonists have been widely recommended for type 2 diabetes management because of their clinically significant health

	Neither	Adopted lifestyle factor with usual care	Use of GLP-1 receptor agonist without lifestyle factor adopted	Use of GLP-1 receptor agonist and lifestyle factor adopted	p value for interaction
Upper 40% of hPDI	1 (ref)	0.89 (0.85–0.93)	0.76 (0.66–0.86)	0.81 (0.70–0.94)	0.054
Activity ≥ 7.5 METs h/week	1 (ref)	0.81 (0.75–0.87)	0.83 (0.74–0.92)	0.61 (0.45–0.81)	0.54
Never smoking	1 (ref)	0.83 (0.78–0.88)	0.84 (0.75–0.94)	0.61 (0.49–0.75)	0.24
No frequent heavy alcohol intake	1 (ref)	0.94 (0.89–0.98)	0.80 (0.69–0.94)	0.77 (0.68–0.88)	0.78
Sleeping 7–9 h/day	1 (ref)	0.93 (0.88–0.97)	0.85 (0.74–0.97)	0.74 (0.64–0.85)	0.49
No opioid use disorder	1 (ref)	0.76 (0.66–0.88)	0.73 (0.38–1.39)	0.62 (0.52–0.74)	0.73
Good stress management	1 (ref)	0.90 (0.84–0.95)	0.79 (0.66–0.95)	0.74 (0.66–0.84)	0.64
Positive social interaction score ≥ 50	1 (ref)	0.92 (0.87–0.97)	0.78 (0.67–0.92)	0.77 (0.68–0.88)	0.46

All data are hazard ratio (95% CI), unless otherwise stated. Adjusted for same covariates as listed in figure 1 and individual low-risk lifestyle (mutually adjusted) besides the stratified one.

Table 5: Joint associations between individual lifestyle factors, use of GLP-1 receptor agonists, and major adverse cardiovascular events

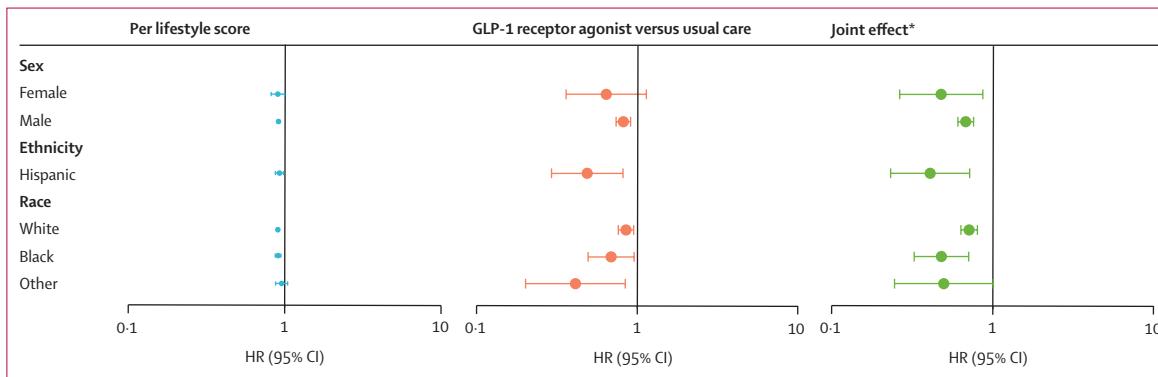


Figure 2: Major adverse cardiovascular events among different subgroups
 HR=hazard ratio. *HR comparing veterans with a composite lifestyle score of 6–8 and use of GLP-1 receptor agonists to veterans who were non-GLP-1 receptor agonist users or received usual care who adopted five or less healthy lifestyle factors (composite lifestyle score 0–3 and 4–5 groups combined because of too few cases in some subgroup populations).

benefits in improving glycaemic control, promoting weight loss, and reducing cardiovascular risk.^{4,5,7,25} However, clinical trial data suggest that a substantial portion of weight loss from GLP-1 receptor agonist use might result from reductions in muscle mass, highlighting the importance of integrating additional lifestyle modifications, particularly the need for physical activity interventions, in obesity and type 2 diabetes management.^{26,27} At least 12 weeks of continuous treatment with GLP-1 receptor agonists is recommended to reach clinically meaningful weight loss that would positively impact overall health.^{26,28} However, observational data indicate low adherence to GLP-1 treatment, with over 30% of individuals discontinuing use within the first 4 weeks and more than half not maintaining their prescribed treatment for at least 12 weeks.²⁹ Evidence also suggests that adding supervised exercise to a GLP-1 receptor agonist treatment enhanced both weight loss and maintenance compared with pharmacotherapy alone, with sustained benefits observed even 1 year after treatment.³⁰ Our study expanded the evaluation of the joint association between lifestyle and GLP-1 receptor agonist use by incorporating a comprehensive assessment of eight lifestyle factors in relation to long-term cardiovascular disease risk in a real-world setting. We found that both lifestyle and GLP-1 receptor agonist use were independently associated with lower MACE risk, and their combination was associated with a greater reduction than either exposure alone.

Other key strengths of our study include the large sample size of participants with type 2 diabetes with diverse socioeconomic and racial and ethnic backgrounds, and the comprehensive assessment of multiple lifestyle factors based on recommendations from the Lifestyle Medicine Research Summit,⁹ which aligns with the American Diabetes Association Professional Practice Committee's⁷ guidance on intensive lifestyle interventions. We also did several sensitivity analyses to minimise potential reverse causation and confounding, and the results were broadly consistent with those of the main analyses.

Several limitations warrant consideration. First, our analyses were based on VHA EHR records, and health-care use outside the VHA system is only incompletely captured. As a result, some non-Veterans Affairs medication use might not have been fully ascertained. Second, our estimation was based on observational data in which lifestyle factors were assessed at baseline, whereas GLP-1 receptor agonist use was updated throughout follow-up. This difference in timing introduces some temporal ambiguity that might limit causal interpretation. Future studies, ideally randomised controlled trials, are warranted to replicate our findings and establish the causal relationship. Third, because our cohort consists of predominantly male veterans, the findings might not be generalisable to other populations. Nonetheless, the findings for female veterans were

similar to those for males, despite a smaller sample size. Fourth, unmeasured confounding might also exist even though we controlled for a wide range of potential confounders. However, only a very strong unmeasured risk factor associated with the combination of healthy lifestyle and GLP-1 receptor agonist and with MACE could plausibly explain our findings.³¹ Finally, although the percentage of participants who adhered to all eight lifestyle factors was relatively small, the continuous, graded reduction in MACE associated with increasing lifestyle scores suggests that any improvement in lifestyle behaviours might confer additional benefits in lowering the risk of cardiovascular disease.

In conclusion, findings from this study of MVP participants indicate that both adherence to a healthy lifestyle and GLP-1 receptor agonist use are independently associated with low risk of MACE among veterans with type 2 diabetes, and their combination is associated with a greater risk reduction than either approach alone. These findings highlight the importance of integrating lifestyle modifications and pharmacotherapy in type 2 diabetes management.

Contributors

Conceptualisation and methodology: X-MTN, YL, SC, FBH. Data curation, analysis, and visualisation: X-MTN, YL, NR, SCH, BL, Y-LH, BRC, DDW, DRG. Original draft writing: X-MTN, YL. Supervision: FBH, PFWF, JMG, WCW, BL, DRG, KC. Writing, review, and editing: all authors. Funding acquisition, investigation, project administration, resources, software, and validation: JMG, PFWF, KC, SCH, Y-LH, BRC. Data verification and access to raw data: X-MTN, YL. Final responsibility for the decision to submit for publication: X-MTN, YL, FBH.

Declaration of interests

SC received consulting fees from Novo Nordisk, Boehringer, AstraZeneca, MSD, Roche, Amgen, Pfizer, and Fresenius; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Novo Nordisk, Janssen-Cilag, J&J, and Novartis; support for attending meetings or travel from Novo Nordisk and Lilly; participated in an advisory board for Novo Nordisk and Lilly; and has stock or stock options for Alifert and Jellynov. FBH received a research grant from Analysis Group. All other authors declare no competing interests.

Data sharing

Data used in this study cannot be shared publicly because of Veterans Affairs' policies regarding data privacy and security. Data contain potentially identifying and sensitive patient information. All relevant summary level data are included in the manuscript. For investigators with appropriate authorisations within the US Department of Veterans Affairs, requests for data access can be made to the corresponding author.

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