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Supplementary Methods

Propensity Score Fine Stratification Weighting

To conduct propensity score fine stratification weighting, within each cohort, the propensity score was estimated for all patients using multivariable logistic regression to predict the probability of initiating a GLP-1 RA vs. the comparator drug. After trimming patients who fell in non-overlapping regions of the propensity score distribution, we generated 50 strata of patients based on the distribution of the propensity score among GLP-1 RA users. Each of these 50 strata contained n_k GLP-1 RA users and m_k comparator drug users, where n and m represent the number of patients and k represents the stratum. The entire cohort contained N GLP-1 RA users and M comparator drug users. In each of the strata, patients using a GLP-1 RA received a weight w_1 of 1 while patients using a comparator drug received a weight w_0 proportional to the number of GLP-1 users in that stratum. The weights were scaled such that the sum of weights of the comparator drug users was equal to the total number of comparator drug users in the cohort.

$$w_1 = 1 \qquad w_{0,k} = \frac{n_k}{m_k} * \frac{M}{N}$$

$$\sum w_1 = N \qquad \sum_{i=1}^{k} w_{0,k} = M$$

A simple example consists of a cohort of 60 GLP-1 RA users and 130 comparator users divided into two strata: stratum 1 with 10 GLP-1 RA drug users and 100 comparator drug users, and stratum 2 with 50 GLP-1 RA users and 30 comparator drug users.

$$n_1 = 10 \qquad m_1 = 100$$

$$n_2 = 50 \qquad m_2 = 30$$

$$N = 60 \qquad M = 130$$

Each GLP-1 RA user would receive a weight of 1. The 100 comparator drug users in stratum 1 would each receive a weight of 0.22 while the 30 comparator drug users in stratum 2 would each receive a weight of 3.6.

$$w_1 = 1 \qquad w_{0,1} = \frac{n_1}{m_1} * \frac{M}{N} = \frac{10}{100} * \frac{130}{60} = 0.22 \qquad w_{0,2} = \frac{n_2}{m_2} * \frac{M}{N} = \frac{50}{30} * \frac{130}{60} = 3.6$$

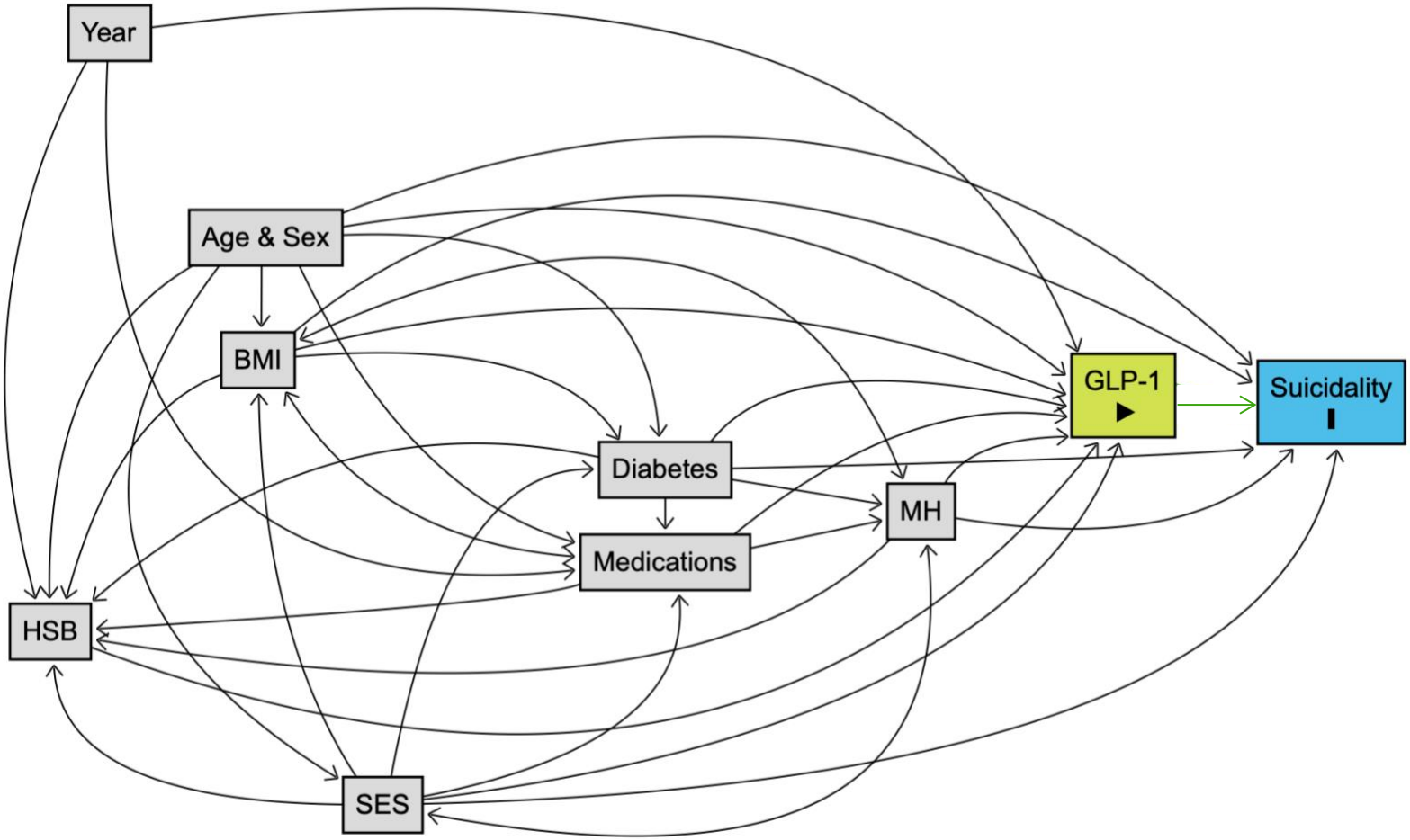
The sum of the weights of the 60 GLP-1 RA users would be 60, while the sum of the weights of the 130 comparator drug users would be 130.

$$\sum w_1 = 1 * 60 = 60 \qquad \sum_{i=1}^{k} w_{0,k} = \sum w_{0,1} + \sum w_{0,2} = 0.22 * 100 + 3.6 * 30 = 22 + 108 = 130$$

Reproducible Code

Reproducible codes for cohort construction, propensity score generation, propensity score fine stratification weighting, and primary analyses can be found on Open Science Framework.

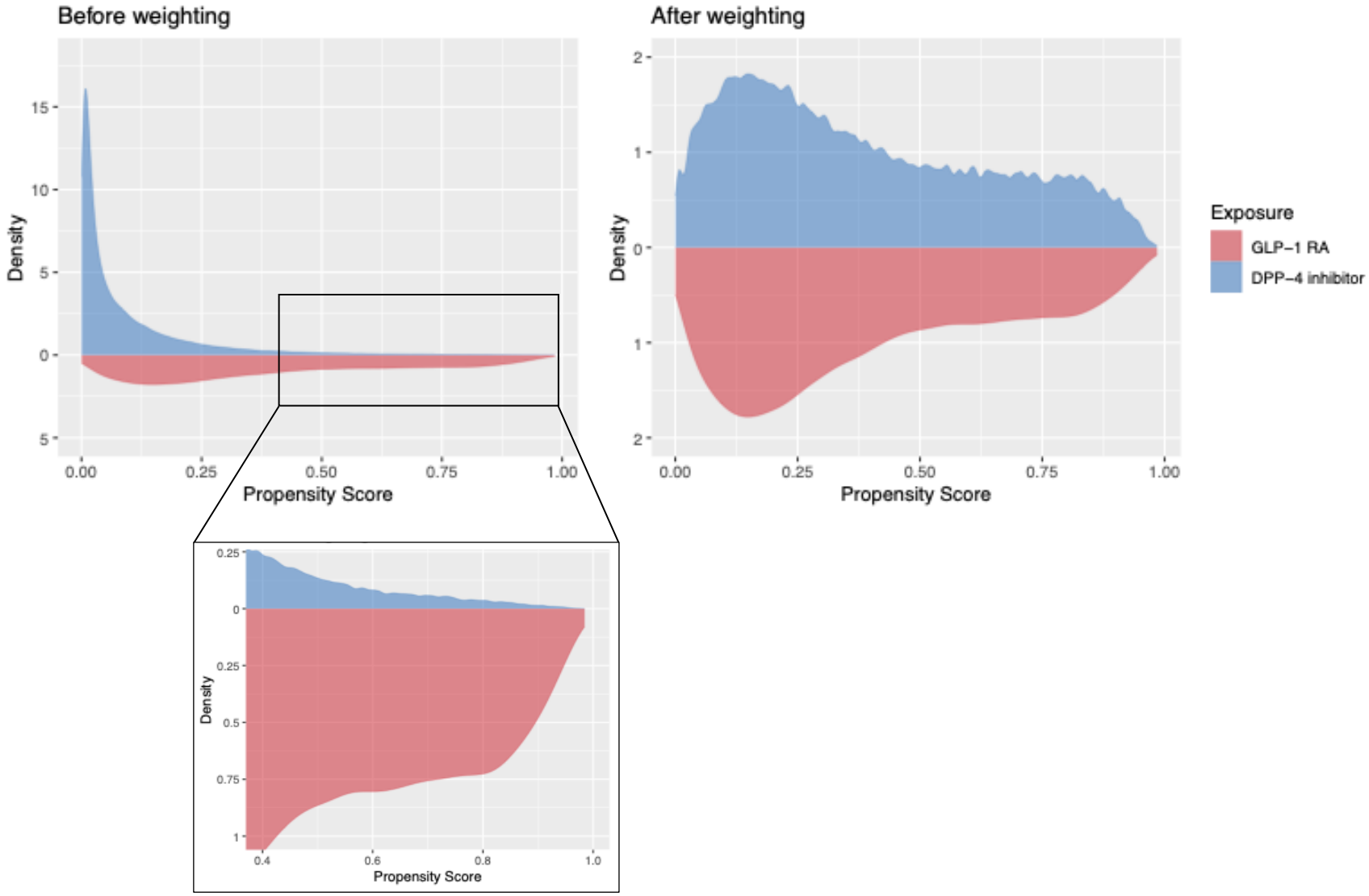
Supplementary Figure S1: Condensed Directed Acyclic Diagram of Exposure, Outcome, and Primary Confounder Groups



Abbreviations: BMI, body mass index; GLP-1, glucagon-like peptide-1 receptor agonist; HSB, health-seeking behaviours; MH, mental health; SES, socioeconomic status

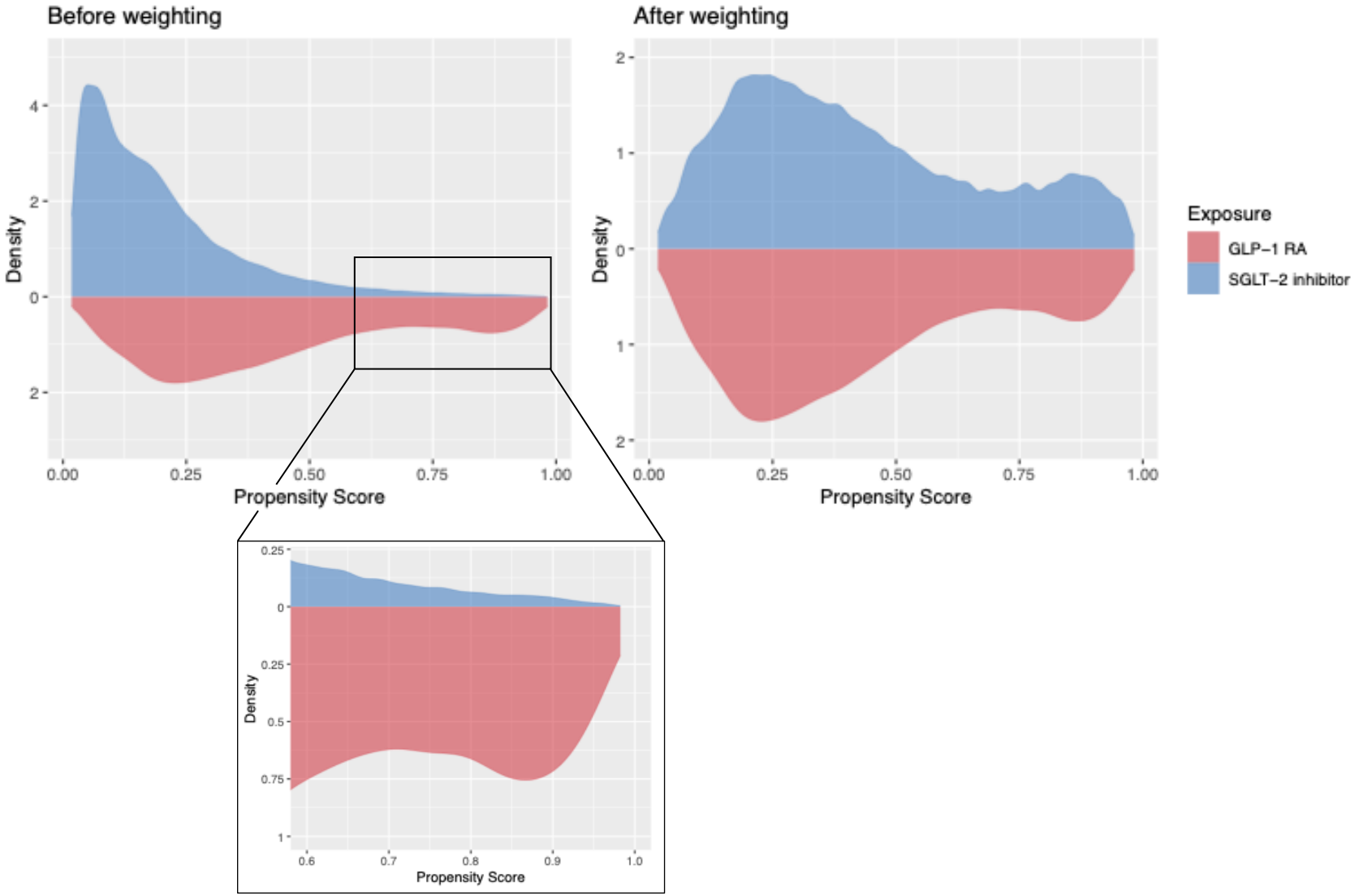
We considered 57 covariates in our causal model, which were condensed into primary confounder groups in this DAG for legibility. Although unmeasured confounding is possible, it is not displayed in this DAG for brevity.

Supplementary Figure S2A: Propensity Score Distribution of GLP-1 RA and DPP-4 Inhibitor Users Before and After Weighting



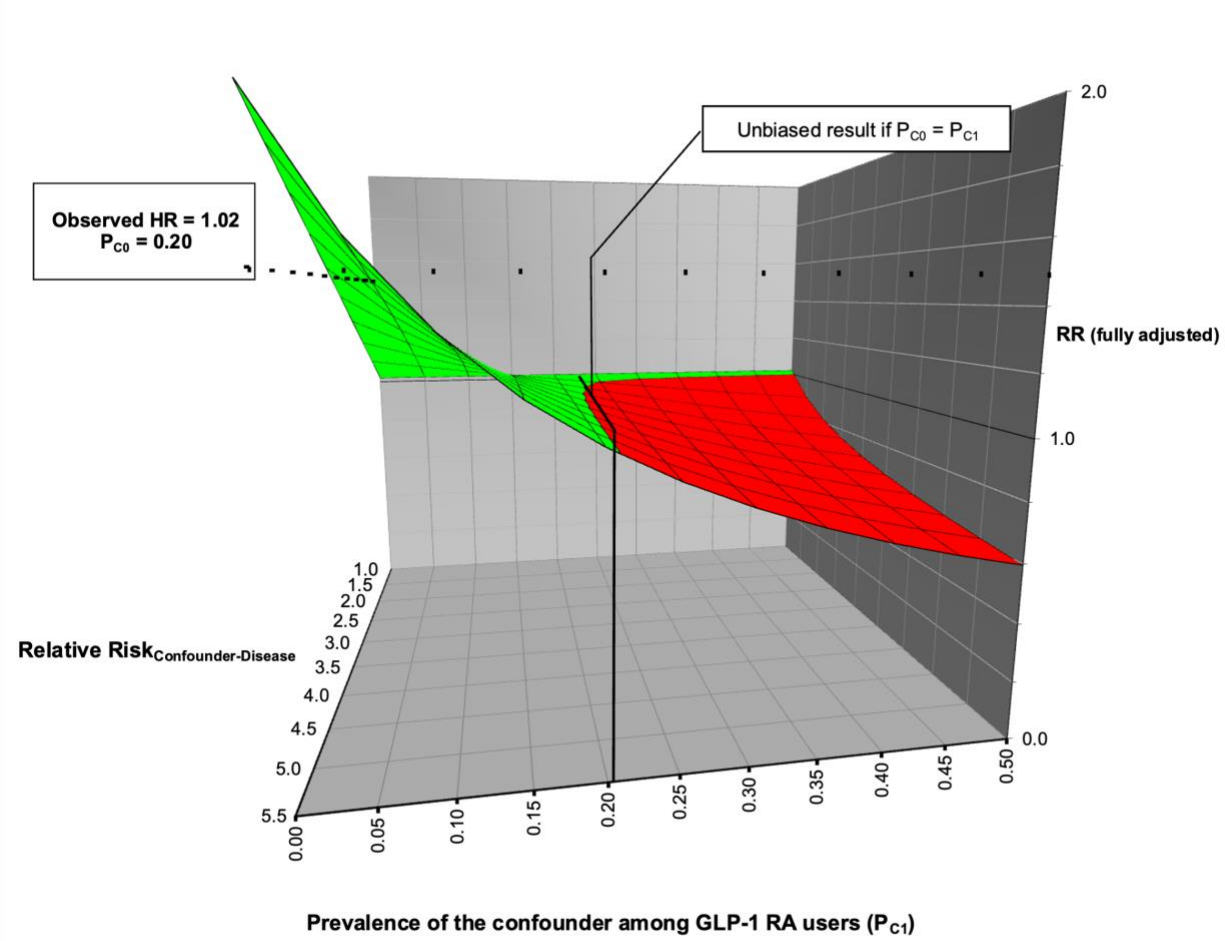
Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist

Supplementary Figure S2B: Propensity Score Distribution of GLP-1 RA and SGLT-2 Inhibitor Users Before and After Weighting



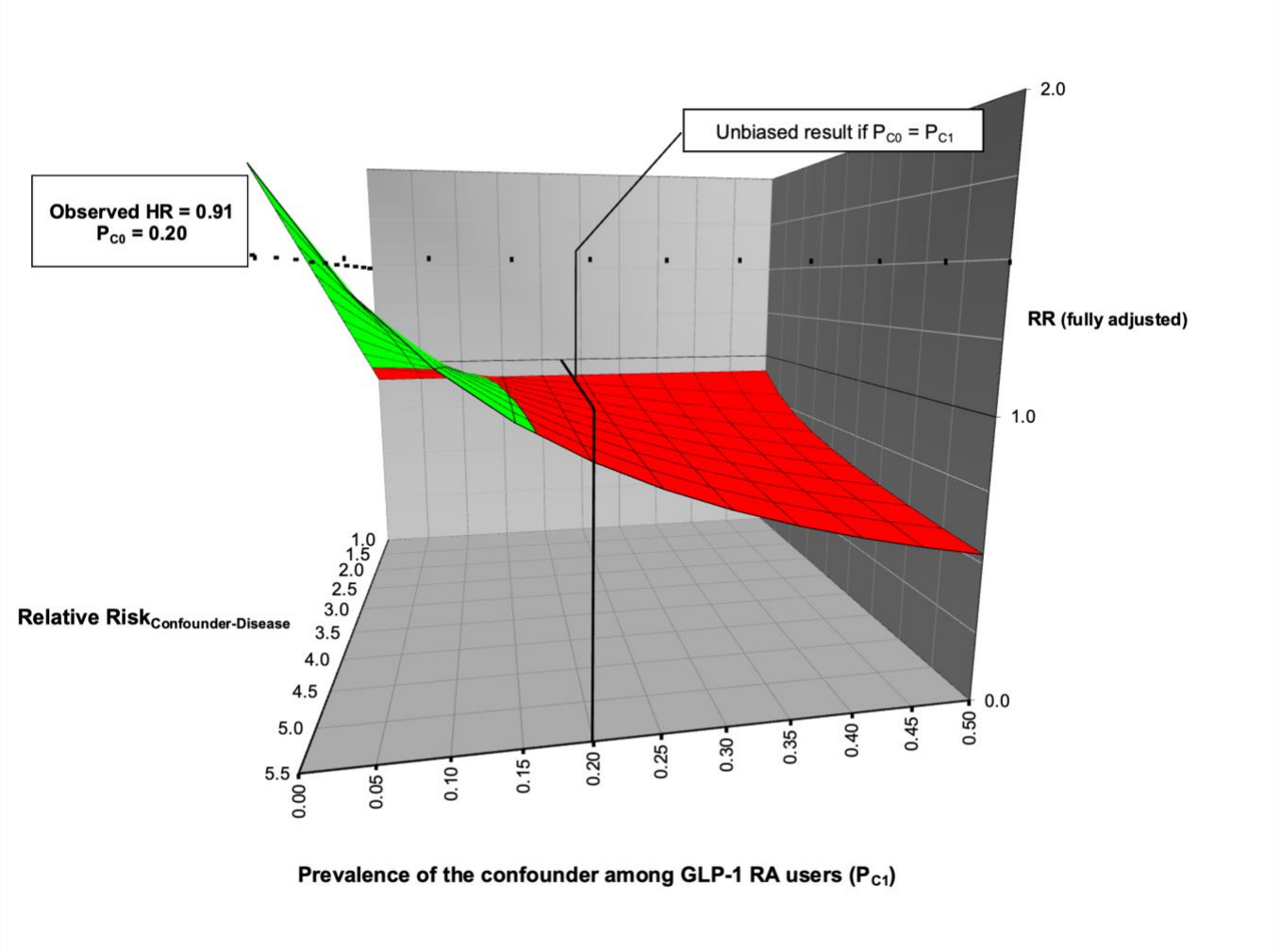
Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2, sodium-glucose cotransporter-2

Supplementary Figure S3A. Array Analysis for Unmeasured Confounding Comparing GLP-1 RAs to DPP-4 Inhibitors



We conducted an array analysis to determine the necessary conditions for an unmeasured variable to confound the observed association. The prevalence of a hypothetical confounder in the comparator group (P_{C0}) was fixed at 20%, while the strength of the confounder-disease association was allowed to range from 1.0 to 5.5 and the prevalence of the confounder among GLP-1 RA users could range from 0% to 100%. An unmeasured confounding variable would need to be highly imbalanced between groups and strongly associated with the outcome to bias the association.

Supplementary Figure S3B. Array Analysis for Unmeasured Confounding Comparing GLP-1 RAs to SGLT-2 Inhibitors



We conducted an array analysis to determine the necessary conditions for an unmeasured variable to confound the observed association. The prevalence of a hypothetical confounder in the comparator group (P_{C0}) was fixed at 20%, while the strength of the confounder-disease association was allowed to range from 1.0 to 5.5 and the prevalence of the confounder among GLP-1 RA users could range from 0% to 100%. An unmeasured confounding variable would need to be highly imbalanced between groups and strongly associated with the outcome to bias the association.

Supplementary Table S1. ICD-10 Code Descriptions	
X60	Intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics
X61	Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
X62	Intentional self-poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified
X63	Intentional self-poisoning by and exposure to other drugs acting on the autonomic nervous system
X64	Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances
X65	Intentional self-poisoning by and exposure to alcohol
X66	Intentional self-poisoning by and exposure to organic solvents and halogenated hydrocarbons and their vapors
X67	Intentional self-poisoning by and exposure to carbon monoxide and other gases and vapors
X67.0	carbon monoxide from combustion engine exhaust
X67.1	carbon monoxide from utility gas
X67.2	carbon monoxide from other domestic fuels
X67.3	carbon monoxide from other sources
X67.4	carbon monoxide from unspecified sources
X67.8	other specified gases and vapors
X67.9	unspecified gases and vapors
X68	Intentional self-poisoning by and exposure to pesticides
X69	Intentional self-poisoning by and exposure to other and unspecified chemicals and noxious substances
X70	Intentional self-harm by hanging, strangulation and suffocation
X71	Intentional self-harm by drowning and submersion
X71.0	while in bathtub
X71.1	while in swimming pool
X71.2	after jump into swimming pool
X71.3	in natural water
X71.8	other
X71.9	unspecified
X72	Intentional self-harm by handgun discharge
X73	Intentional self-harm by rifle, shotgun and larger firearm discharge
X73.0	shotgun

X73.1 hunting rifle
X73.2 machine gun
X73.8 other larger firearm
X73.9 unspecified
X74 Intentional self-harm by other and unspecified firearm and gun discharge
X74.0 gas, air or spring-operated guns
X74.8 other firearm
X74.9 unspecified firearm
X75 Intentional self-harm by explosive material
X76 Intentional self-harm by smoke, fire and flames
X77 Intentional self-harm by steam, hot vapors and hot objects
X77.0 steam or hot vapors
X77.1 hot tap water
X77.2 other hot fluids
X77.3 hot household appliances
X77.8 other hot objects
X77.9 unspecified hot objects
X78 Intentional self-harm by sharp object
X78.0 sharp glass
X78.1 knife
X78.2 sword or dagger
X78.8 other sharp object
X78.9 unspecified sharp object
X79 Intentional self-harm by blunt object
X80 Intentional self-harm by jumping from a high place
X81 Intentional self-harm by jumping or lying in front of moving object
X81.0 motor vehicle
X81.1 (subway) train
X81.8 other moving object

X82 Intentional self-harm by crashing of motor vehicle
X82.0 collision of motor vehicle with other motor vehicle
X82.1 collision of motor vehicle with train
X82.2 collision of motor vehicle with tree
X82.8 other crashing of motor vehicle
X83 Intentional self-harm by other specified means
X83.0 crashing of aircraft
X83.1 electrocution
X83.2 exposure to extremes of cold
X83.8 other specified means
X84 Intentional self-harm by unspecified means
Y87.0 Sequelae of intentional self-harm

Supplementary Table S2. Covariate Lookback Periods and Data Sources			
Covariate	**Time of measurement**	**Data source**	**Example code list**
Age	Cohort entry	CPRD	N/A
Sex	Cohort entry	CPRD	N/A
Quintile of Index of Multiple Deprivation	Cohort entry	CPRD	N/A
Body mass index	Cohort entry	CPRD	N/A
Hemoglobin A1c	Cohort entry	CPRD	Link
Duration of diabetes in years	Cohort entry	CPRD, HES	Link
Microvascular complications			
Nephropathy	Any time preceding cohort entry	CPRD, HES	Link
Neuropathy	Any time preceding cohort entry	CPRD, HES	Link
Retinopathy	Any time preceding cohort entry	CPRD, HES	Link
Macrovascular complications			
Myocardial infarction	Any time preceding cohort entry	CPRD, HES	Link
Stroke	Any time preceding cohort entry	CPRD, HES	Link
Peripheral arteriopathy	Any time preceding cohort entry	CPRD, HES	Link
Previous use of antidiabetic drugs			
Metformin	Year preceding cohort entry	CPRD	Link
Thiazolidinediones	Year preceding cohort entry	CPRD	Link
Sulfonylureas	Year preceding cohort entry	CPRD	Link
Meglitinides	Year preceding cohort entry	CPRD	Link
Alpha-glucosidase inhibitors	Year preceding cohort entry	CPRD	Link
Insulin	Year preceding cohort entry	CPRD	Link
DPP-4 inhibitors	Year preceding cohort entry	CPRD	Link
SGLT-2 inhibitors	Year preceding cohort entry	CPRD	Link
Mental health disorders			
Depression	Any time preceding cohort entry	CPRD, HES	Link
Anxiety	Any time preceding cohort entry	CPRD, HES	Link
Bipolar disorder	Any time preceding cohort entry	CPRD, HES	Link
Psychosis	Any time preceding cohort entry	CPRD, HES	Link
Schizophrenia	Any time preceding cohort entry	CPRD, HES	Link

Obsessive-compulsive disorder	Any time preceding cohort entry	CPRD, HES	Link
Attention deficit disorder	Any time preceding cohort entry	CPRD, HES	Link
Borderline personality disorder	Any time preceding cohort entry	CPRD, HES	
Eating disorder	Any time preceding cohort entry	CPRD, HES	Link
Post-traumatic stress disorder	Any time preceding cohort entry	CPRD, HES	Link
History of self-harm or suicide attempt	Any time preceding cohort entry	CPRD, HES	Link
History of suicidal ideation	Any time preceding cohort entry	CPRD, HES	
Other comorbidities			
Insomnia	Any time preceding cohort entry	CPRD, HES	Link
Epilepsy	Any time preceding cohort entry	CPRD, HES	Link
Dementia	Any time preceding cohort entry	CPRD, HES	Link
Chronic pain	Any time preceding cohort entry	CPRD, HES	Link
History of cancer	Any time preceding cohort entry	CPRD, HES	Link
Substance use	Any time preceding cohort entry	CPRD, HES	Link
Smoking status	Cohort entry	CPRD, HES	Link
Presence of alcohol-related disorders	Any time preceding cohort entry	CPRD, HES	Link
Medication use			
ACE inhibitors	Year preceding cohort entry	CPRD	Link
Angiotensin receptor blockers	Year preceding cohort entry	CPRD	Link
Beta blockers	Year preceding cohort entry	CPRD	Link
Calcium channel blockers	Year preceding cohort entry	CPRD	Link
Thiazides	Year preceding cohort entry	CPRD	Link
Other diuretics	Year preceding cohort entry	CPRD	Link
Antiarrhythmic agents	Year preceding cohort entry	CPRD	
Antiplatelet agents	Year preceding cohort entry	CPRD	Link
Statins	Year preceding cohort entry	CPRD	Link
Fibrates	Year preceding cohort entry	CPRD	
Proton pump inhibitors	Year preceding cohort entry	CPRD	Link
NSAIDs	Year preceding cohort entry	CPRD	Link
Health-seeking behaviors			
Mammography	Year preceding cohort entry	CPRD, HES	Link

Fecal occult blood testing or colonoscopy	Year preceding cohort entry	CPRD, HES	Link
Prostate-specific antigen testing	Year preceding cohort entry	CPRD, HES	Link
Influenza vaccination	Year preceding cohort entry	CPRD, HES	Link
Pneumococcal vaccination	Year preceding cohort entry	CPRD, HES	Link

Abbreviations: ACE, angiotensin converting enzyme; CPRD, Clinical Practice Research Datalink; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HES, Hospital Episode Statistics; N/A, not applicable (covariate identified directly through CPRD data); NSAID, non-steroidal anti-inflammatory drug; SGLT-2, sodium-glucose cotransporter-2

Supplementary Table S3: Comparison Between Target Trial and Emulated Trial Using Real-World Data		
Study characteristic	**Target trial**	**Emulated trial using real-world data**
Eligibility criteria	Adult patients with a diagnosis of type 2 diabetes, without history of end-stage renal disease or multiple endocrine neoplasia syndrome, and without prior use of either study drug.	Same as hypothetical trial, but with the additional requirement of a one-year history in the database.
Treatment strategies	Initiation of a GLP-1 RA or a comparator medication (DPP-4 inhibitor or SGLT-2 inhibitor), with continuation until any of the study outcomes.	Same as hypothetical trial.
Assignment procedures	Patients are randomly assigned to one of the two treatment strategies.	Randomization is emulated by conducting propensity score fine stratification weighting accounting for 57 potential confounding variables.
Follow-up	From initiation of treatment strategy until the first of an outcome, death from any cause other than suicide, end of the study period, or loss to follow-up.	Same as hypothetical trial, but with censoring at study drug switching or discontinuation.
Outcomes	Diagnosis of suicidal ideation, self-harm, or completed suicide according to the ICD-10 codes listed in **Supplementary Table 1**.	Same as hypothetical trial.
Causal contrast of interest	Intention-to-treat effect.	On-treatment effect.
Statistical methods	Estimated via Cox proportional hazards regression.	Estimated via Cox proportional hazards regression with propensity score fine stratification weighting to account for the influence of confounding variables.

Supplementary Table S4. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with DPP-4 Inhibitors; Stratification by Individual Drug

Exposure	No. of patients	Events	Person-years	Crude IR [a]	Weighted IR (95% CI) [a,b]	Crude HR (95% CI)	Weighted HR (95% CI) [b]
DPP-4 inhibitors	126,725	549	245,273	2.2	5.4 (5.1 to 5.8)	1.00 [Reference]	1.00 [Reference]
Dulaglutide	6,046	54	8,497	6.4	6.4 (4.8 to 8.3)	2.65 (2.00 to 3.51)	1.18 (0.84 to 1.66)
DPP-4 inhibitors	228,228	1,077	592,352	1.8	3.1 (2.9 to 3.2)	1.00 [Reference]	1.00 [Reference]
Exenatide	12,725	93	25,546	3.6	3.6 (2.9 to 4.5)	1.93 (1.56 to 2.38)	1.06 (0.75 to 1.49)
DPP-4 inhibitors	221,766	1,056	571,053	1.9	3.8 (3.6 to 3.9)	1.00 [Reference]	1.00 [Reference]
Liraglutide	13,018	105	29,408	3.6	3.6 (2.9 to 4.3)	1.88 (1.54 to 2.30)	0.92 (0.72 to 1.17)
DPP-4 inhibitors	148,662	713	338,107	2.1	4.3 (4.1 to 4.6)	1.00 [Reference]	1.00 [Reference]
Lixisenatide	1,816	14	2,733	5.1	5.1 (2.8 to 8.6)	2.27 (1.34 to 3.86)	1.11 (0.63 to 1.95)
DPP-4 inhibitors	32,621	97	33,135	2.9	5.8 (4.9 to 6.7)	1.00 [Reference]	1.00 [Reference]
Semaglutide	2,460	12	1,940	6.2	6.2 (3.2 to 10.8)	2.02 (1.11 to 3.69)	1.07 (0.54 to 2.12)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate

[a] Per 1,000 person-years.

[b] The models were weighted using propensity score fine stratification. Separate analyses were conducted for each comparison.

Supplementary Table S5. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with DPP-4 Inhibitors; Interaction With Physiological Characteristics

Exposure	No. of patients	Events	Person-years	Weighted IR (95% CI) [a,b]	Weighted HR (95% CI) [b,c]
Age					
18-30 years					
DPP-4 inhibitors	1,365	16	2,087	13.6 (11.2 to 17.1)	1.00 [Reference]
GLP-1 RAs	772	16	913	17.5 (10.7 to 28.6)	1.18 (0.43 to 3.25)
31–50 years					
DPP-4 inhibitors	38,284	382	89,009	7.1 (6.7 to 7.6)	1.00 [Reference]
GLP-1 RAs	10,377	147	20,679	7.1 (6.1 to 8.4)	0.98 (0.74 to 1.29)
51–70 years					
DPP-4 inhibitors	118,986	526	324,612	2.5 (2.4 to 2.7)	1.00 [Reference]
GLP-1 RAs	21,592	131	48,949	2.7 (2.3 to 3.2)	1.03 (0.79 to 1.36)
>70 years					
DPP-4 inhibitors	75,393	163	183,563	1.5 (1.2 to 1.8)	1.00 [Reference]
GLP-1 RAs	3,341	7	6,795	1.0 (0.5 to 2.2)	0.68 (0.28 to 1.65)
Sex					
Female					
DPP-4 inhibitors	99,764	507	244,750	4.6 (4.3 to 4.9)	1.00 [Reference]
GLP-1 RAs	17,509	175	36,911	4.7 (4.1 to 5.5)	1.01 (0.78 to 1.30)
Male					
DPP-4 inhibitors	134,264	580	354,521	2.9 (2.7 to 3.2)	1.00 [Reference]
GLP-1 RAs	18,573	126	40,425	3.1 (2.6 to 3.7)	1.03 (0.78 to 1.35)
Body mass index [d]					
<30 kg/m^2					
DPP-4 inhibitors	100,640	342	258,010	2.6 (2.1 to 3.2)	1.00 [Reference]
GLP-1 RAs	2,800	19	5,189	3.7 (2.3 to 5.7)	1.33 (0.78 to 2.27)

30–34.9 kg/m^2					
DPP-4 inhibitors	69,745	354	185,509	3.4 (3.1 to 3.7)	1.00 [Reference]
GLP-1 RAs	9,086	62	19,321	3.2 (2.5 to 4.1)	0.91 (0.64 to 1.31)
35–39.9 kg/m^2					
DPP-4 inhibitors	36,970	211	94,341	3.5 (3.2 to 3.8)	1.00 [Reference]
GLP-1 RAs	10,559	85	23,139	3.7 (3.0 to 4.5)	1.03 (0.73 to 1.44)
≥40 kg/m^2					
DPP-4 inhibitors	24,651	164	57,595	4.4 (4.1 to 4.7)	1.00 [Reference]
GLP-1 RAs	12,953	125	28,316	4.4 (3.7 to 5.3)	1.00 (0.72 to 1.39)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate

[a] Per 1,000 person-years.

[b] The models were weighted using propensity score fine stratification.

[c] Hazard ratios for each of the potential effect modifiers were calculated by including an interaction term between the exposure and the effect modifier in regression models. Separate analyses were run for each effect modifier but are included in the same table for brevity.

[d] Unknown BMI category was included in the analysis but not presented in the table.

Supplementary Table S6. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with DPP-4 Inhibitors; Interaction With Mental Health History

Exposure	No. of patients	Events	Person-years	Weighted IR (95% CI) [a,b]	Weighted HR (95% CI) [b,c]
History of self-harm or suicide attempt					
Without history					
DPP-4 inhibitors	228,575	776	588,367	2.3 (2.2 to 2.4)	1.00 [Reference]
GLP-1 RAs	34,497	205	74,573	2.9 (2.4 to 3.2)	1.17 (0.93 to 1.48)
With history					
DPP-4 inhibitors	5,453	311	10,904	46.9 (43.8 to 50.3)	1.00 [Reference]
GLP-1 RAs	1,585	96	2,764	34.7 (28.4 to 42.4)	0.74 (0.54 to 1.01)
History of suicidal ideation					
Without history					
DPP-4 inhibitors	231,694	899	594,903	2.9 (2.7 to 3.0)	1.00 [Reference]
GLP-1 RAs	35,316	233	76,075	3.1 (2.7 to 3.5)	1.05 (0.85 to 1.30)
With history					
DPP-4 inhibitors	2,334	188	4,368	59.9 (54.7 to 65.5)	1.00 [Reference]
GLP-1 RAs	766	68	1,261	53.9 (42.5 to 68.4)	0.92 (0.62 to 1.34)
History of depression					
Without history					
DPP-4 inhibitors	155,719	253	415,752	0.9 (0.8 to 1.0)	1.00 [Reference]
GLP-1 RAs	19,340	50	43,953	1.1 (0.9 to 1.5)	1.31 (0.82 to 2.09)
With history					
DPP-4 inhibitors	78,309	834	183,519	7.6 (7.2 to 7.9)	1.00 [Reference]
GLP-1 RAs	16,742	251	33,384	7.5 (6.6 to 8.5)	0.97 (0.79 to 1.19)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate

[a] Per 1,000 person-years.

[b] The models were weighted using propensity score fine stratification.

[c] Hazard ratios for each of the potential effect modifiers were calculated by including an interaction term between the exposure and the effect modifier in regression models. Separate analyses were run for each effect modifier but are included in the same table for brevity.

Supplementary Table S7. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with DPP-4 Inhibitors; Interaction With Quintile of Index of Multiple Deprivation

Exposure [a]	No. of patients	Events	Person-years	Weighted IR (95% CI) [b,c]	Weighted HR (95% CI) [c]
Q1 (least deprived)					
DPP-4 inhibitors	36,039	98	95,165	2.9 (2.6 to 3.3)	1.00 [Reference]
GLP-1 RAs	5,430	30	12,172	2.5 (1.7 to 3.5)	0.82 (0.44 to 1.54)
Q2					
DPP-4 inhibitors	41,446	150	107,880	3.1 (2.8 to 3.5)	1.00 [Reference]
GLP-1 RAs	6,271	42	14,104	3.0 (2.2 to 4.0)	0.95 (0.56 to 1.61)
Q3					
DPP-4 inhibitors	45,048	167	115,155	2.4 (2.1 to 2.7)	1.00 [Reference]
GLP-1 RAs	6,889	66	14,615	4.5 (3.6 to 5.8)	1.85 (1.25 to 2.73)
Q4					
DPP-4 inhibitors	53,866	260	136,887	4.2 (3.9 to 4.6)	1.00 [Reference]
GLP-1 RAs	7,976	72	16,666	4.3 (3.4 to 5.4)	0.99 (0.68 to 1.45)
Q5 (most deprived)					
DPP-4 inhibitors	57,467	409	143,799	5.2 (4.8 to 5.6)	1.00 [Reference]
GLP-1 RAs	9,495	91	19,742	4.6 (3.8 to 5.7)	0.87 (0.64 to 1.19)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; Q, quintile

[a] Unknown socioeconomic status was included in the analysis, but not presented in the table.

[b] Per 1,000 person-years.

[c] The models were weighted using propensity score fine stratification.

Supplementary Table S8: Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with DPP-4 Inhibitors; Interaction with Decile of Propensity Score

Exposure	Mean PS in decile	No. of patients	Events	Person-years	Weighted IR (95% CI) [a,b]	Weighted HR (95% CI) [b,c]
D1						
DPP-4 inhibitors	0.03	153,767	525	404,192	1.6 (1.3 to 2.0)	1.00 [Reference]
GLP-1 RAs		3,608	19	7,807	2.4 (1.5 to 3.8)	1.42 (0.89 to 2.26)
D2						
DPP-4 inhibitors	0.11	29,136	181	76,199	2.4 (2.0 to 2.8)	1.00 [Reference]
GLP-1 RAs		3,608	24	7,864	3.1 (2.0 to 4.5)	1.22 (0.80 to 1.88)
D3						
DPP-4 inhibitors	0.17	16,516	120	41,533	2.9 (2.5 to 3.4)	1.00 [Reference]
GLP-1 RAs		3,608	23	8,051	2.9 (1.8 to 4.3)	0.96 (0.61 to 1.50)
D4						
DPP-4 inhibitors	0.22	11,344	85	27,528	3.2 (2.7 to 3.7)	1.00 [Reference]
GLP-1 RAs		3,609	27	8,036	3.4 (2.2 to 4.9)	1.03 (0.67 to 1.58)
D5						
DPP-4 inhibitors	0.29	8,185	56	18,592	3.0 (2.6 to 3.6)	1.00 [Reference]
GLP-1 RAs		3,608	31	7,891	3.9 (2.7 to 5.6)	1.26 (0.81 to 1.96)
D6						
DPP-4 inhibitors	0.37	5,812	41	12,584	3.3 (2.8 to 3.8)	1.00 [Reference]
GLP-1 RAs		3,608	37	7,578	4.9 (3.4 to 6.7)	1.46 (0.93 to 2.28)

D7						
DPP-4 inhibitors	0.47	4,181	23	8,768	2.7 (2.2 to 3.2)	1.00 [Reference]
GLP-1 RAs		3,609	24	7,745	3.1 (2.0 to 4.6)	1.15 (0.65 to 2.04)
D8						
DPP-4 inhibitors	0.59	2,539	29	5,019	6.0 (5.3 to 6.7)	1.00 [Reference]
GLP-1 RAs		3,608	36	7,546	4.8 (3.3 to 6.6)	0.80 (0.49 to 1.31)
D9						
DPP-4 inhibitors	0.71	1,660	12	3,198	4.1 (3.6 to 4.8)	1.00 [Reference]
GLP-1 RAs		3,608	34	7,230	4.7 (3.3 to 6.6)	1.13 (0.58 to 2.20)
D10						
DPP-4 inhibitors	0.86	888	15	1,657	10.3 (9.4 to 11.3)	1.00 [Reference]
GLP-1 RAs		3,608	46	7,587	6.1 (4.4 to 8.1)	0.60 (0.34 to 1.09)

Abbreviations: CI, confidence interval; D, decile; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; PS, propensity score

[a] Per 1,000 person-years.

[b] The models were weighted using propensity score fine stratification.

Supplementary Table S9. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with DPP-4 Inhibitors; Sensitivity Analyses

Exposure	No. of patients	Events	Person-years	Crude IR [a]	Weighted IR (95% CI) [a,b]	Crude HR (95% CI)	Weighted HR (95% CI) [b]
60-day grace period							
DPP-4 inhibitors	234,028	970	535,090	1.8	3.8 (3.7 to 4.0)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	36,082	249	63,695	3.9	3.9 (3.4 to 4.4)	2.06 (1.79 to 2.37)	0.98 (0.80 to 1.19)
120-day grace period							
DPP-4 inhibitors	234,028	1,154	634,144	1.8	3.8 (3.6 to 3.9)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	36,082	329	84,759	3.9	3.9 (3.5 to 4.3)	2.08 (1.84 to 2.35)	1.01 (0.85 to 1.21)
Intention-to-treat analysis [c]							
DPP-4 inhibitors	234,028	535	222,116	2.4	5.4 (5.1 to 5.7)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	36,082	178	34,198	5.2	5.2 (4.5 to 6.0)	2.16 (1.82 to 2.56)	0.96 (0.75 to 1.23)
Multiple imputation							
DPP-4 inhibitors	233,960	1,087	599,154	1.8	3.8 (3.6 to 3.9)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	36,082	301	77,337	3.9	3.9 (3.5 to 4.4)	2.08 (1.83 to 2.36)	1.01 (0.84 to 1.22)
Including diagnoses of the outcome captured in the CPRD database							
DPP-4 inhibitors	234,028	1,177	599,098	2.0	4.1 (3.9 to 4.3)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	36,082	331	77,289	4.3	4.3 (3.8 to 4.8)	2.11 (1.87 to 2.38)	1.03 (0.86 to 1.23)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate

[a] Per 1,000 person-years.

[b] The models were weighted using propensity score fine stratification.

[c] Patients were censored by the end of the first year.

Supplementary Table S10. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with DPP-4 Inhibitors; Inverse Probability of Censoring Weighting

Exposure	Events	Person-times	Crude IR [a]	Weighted IR (95% CI) [a,b]	Crude HR (95% CI)	Weighted HR (95% CI)[b]
DPP-4 inhibitors	1,087	599,271	1.8	4.8 (4.7 to 5.0)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	301	77,337	3.9	4.9 (4.4 to 5.4)	2.08 (1.83 to 2.36)	0.92 (0.66 to 1.29)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate

[a] Per 1,000 person-time intervals (90-day interval).

[b] The models were weighted using propensity score fine stratification and inverse probability of censoring weights.

Supplementary Table S11. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with SGLT-2 Inhibitors; Stratification by Individual Drug

Exposure	No. of patients	Events	Person-years	Crude IR [a]	Weighted IR (95% CI) [a,b]	Crude HR (95% CI)	Weighted HR (95% CI) [b]
SGLT-2 inhibitors	89,436	407	149,230	2.7	4.8 (4.5 to 5.2)	1.00 [Reference]	1.00 [Reference]
Dulaglutide	8324	53	11,821	4.5	4.5 (3.4 to 5.9)	1.58 (1.19 to 2.11)	0.92 (0.67 to 1.27)
SGLT-2 inhibitors	94,821	454	167,555	2.7	4.4 (4.1 to 4.6)	1.00 [Reference]	1.00 [Reference]
Exenatide	4,190	26	7,055	3.7	3.7 (2.4 to 5.4)	1.36 (0.92 to 2.02)	0.73 (0.44 to 1.21)
SGLT-2 inhibitors	96,151	454	168,385	2.7	4.6 (4.3 to 4.9)	1.00 [Reference]	1.00 [Reference]
Liraglutide	13,657	110	25,452	4.3	4.3 (3.6 to 5.2)	1.62 (1.31 to 1.99)	0.90 (0.68 to 1.20)
SGLT-2 inhibitors	93,765	452	166,860	2.7	3.4 (3.3 to 3.7)	1.00 [Reference]	1.00 [Reference]
Lixisenatide	3,341	16	4,675	3.4	3.4 (2.0 to 5.6)	1.22 (0.74 to 2.02)	0.90 (0.53 to 1.53)
SGLT-2 inhibitors	36,493	115	34,719	3.3	6.6 (5.7 to 7.5)	1.00 [Reference]	1.00 [Reference]
Semaglutide	2,796	17	2,256	7.5	7.5 (4.4 to 12.1)	2.18 (1.31 to 3.63)	1.14 (0.66 to 1.97)

Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; SGLT-2, sodium-glucose cotransporter-2

[a] Per 1,000 person-years.

[b] The models were weighted using propensity score fine stratification. Separate analyses were conducted for each comparison.

Supplementary Table S12. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with SGLT-2 Inhibitors; Interaction With Physiological Characteristics

Exposure	No. of patients	Events	Person-years	Weighted IR (95% CI) [a,b]	Weighted HR (95% CI) [b,c]
Age					
18-30 years					
SGLT-2 inhibitors	915	14	1,160	20.1 (15.2 to 26.6)	1.00 [Reference]
GLP-1 RAs	615	14	668	21.0 (12.4 to 35.4)	0.97 (0.38 to 2.48)
31–50 years					
SGLT-2 inhibitors	21,995	178	37,521	7.5 (6.7 to 8.3)	1.00 [Reference]
GLP-1 RAs	7,809	101	12,367	8.2 (6.7 to 9.9)	1.04 (0.75 to 1.45)
51–70 years					
SGLT-2 inhibitors	60,031	249	109,069	3.8 (3.4 to 4.1)	1.00 [Reference]
GLP-1 RAs	19,148	119	34,736	3.4 (2.9 to 4.1)	0.88 (0.65 to 1.20)
>70 years					
SGLT-2 inhibitors	13,271	13	20,635	1.5 (1.1 to 2.1)	1.00 [Reference]
GLP-1 RAs	4,764	6	7,849	0.8 (0.3 to 1.7)	0.50 (0.13 to 1.92)
Sex					
Female					
SGLT-2 inhibitors	38,631	196	64,697	4.5 (4.1 to 5.0)	1.00 [Reference]
GLP-1 RAs	15,623	136	26,717	5.1 (4.3 to 6.0)	1.10 (0.82 to 1.48)
Male					
SGLT-2 inhibitors	57,581	258	103,688	4.7 (4.3 to 5.1)	1.00 [Reference]
GLP-1 RAs	16,713	104	28,903	3.6 (3.0 to 4.4)	0.74 (0.54 to 1.01)
Body mass index [d]					
<30 kg/m^2					
SGLT-2 inhibitors	33,525	111	56,611	2.4 (1.8 to 3.2)	1.00 [Reference]
GLP-1 RAs	3,432	22	5,106	4.3 (2.8 to 6.5)	1.72 (1.02 to 2.89)

30–34.9 kg/m^2					
SGLT-2 inhibitors	30,884	128	56,299	3.2 (2.8 to 3.7)	1.00 [Reference]
GLP-1 RAs	9,375	72	15,882	4.5 (3.6 to 5.7)	1.34 (0.91 to 1.98)
35–39.9 kg/m^2					
SGLT-2 inhibitors	18,003	112	32,275	5.0 (4.4 to 5.6)	1.00 [Reference]
GLP-1 RAs	9,342	52	16,673	3.1 (2.4 to 4.1)	0.61 (0.41 to 0.91)
≥40 kg/m^2					
SGLT-2 inhibitors	13,149	97	22,244	6.1 (5.5 to 6.8)	1.00 [Reference]
GLP-1 RAs	9,676	84	17,107	4.9 (4.0 to 6.1)	0.78 (0.53 to 1.16)

Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; SGLT-2, sodium-glucose cotransporter-2

[a] Per 1,000 person-years.

[b] The models were weighted using propensity score fine stratification.

[c] Hazard ratios for each of the potential effect modifiers were calculated by including an interaction term between the exposure and the effect modifier in regression models. Separate analyses were run for each effect modifier but are included in the same table for brevity.

[d] Unknown BMI category was included in the analysis but not presented in the table.

Supplementary Table S13. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with SGLT-2 Inhibitors; Interaction With Mental Health History

Exposure	No. of patients	Events	Person-years	Weighted IR (95% CI) [a,b]	Weighted HR (95% CI) [b,c]
History of self-harm or suicide attempt					
Without history					
SGLT-2 inhibitors	93,213	322	163,855	3.2 (3.0 to 3.5)	1.00 [Reference]
GLP-1 RAs	30,844	160	53,403	3.0 (2.6 to 3.5)	0.90 (0.70 to 1.17)
With history					
SGLT-2 inhibitors	2,999	132	4,529	37.8 (33.7 to 42.5)	1.00 [Reference]
GLP-1 RAs	1,492	80	2,217	36.1 (29.0 to 44.9)	0.93 (0.63 to 1.37)
History of suicidal ideation					
Without history					
SGLT-2 inhibitors	94,670	360	166,192	3.4 (3.1 to 3.6)	1.00 [Reference]
GLP-1 RAs	31,626	180	54,650	3.3 (2.9 to 3.8)	0.96 (0.75 to 1.22)
With history					
SGLT-2 inhibitors	1,542	94	2,192	77.7 (68.6 to 88.1)	1.00 [Reference]
GLP-1 RAs	710	60	970	61.9 (48.0 to 79.7)	0.78 (0.50 to 1.22)
History of depression					
Without history					
SGLT-2 inhibitors	60,175	79	108,181	1.6 (1.4 to 1.9)	1.00 [Reference]
GLP-1 RAs	17,190	29	30,782	0.9 (0.7 to 1.4)	0.57 (0.32 to 1.00)
With history					
SGLT-2 inhibitors	36,037	375	60,203	8.1 (7.5 to 8.7)	1.00 [Reference]
GLP-1 RAs	15,146	211	24,838	8.5 (7.4 to 9.7)	1.01 (0.80 to 1.29)

Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; SGLT-2, sodium-glucose cotransporter-2

[a] Per 1,000 person-years.

[b] The models were weighted using propensity score fine stratification.

[c] Hazard ratios for each of the potential effect modifiers were calculated by including an interaction term between the exposure and the effect modifier in regression models. Separate analyses were run for each effect modifier but are included in the same table for brevity.

Supplementary Table S14. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with SGLT-2 Inhibitors; Interaction With Quintile of Index of Multiple Deprivation

Exposure [a]	No. of patients	Events	Person-years	Weighted IR (95% CI) [b,c]	Weighted HR (95% CI) [c]
Q1 (least deprived)					
SGLT-2 inhibitors	15,112	45	26,959	2.3 (1.8 to 2.9)	1.00 [Reference]
GLP-1 RAs	4,696	24	8,185	2.9 (2.0 to 4.4)	1.25 (0.60 to 2.61)
Q2					
SGLT-2 inhibitors	16,965	83	30,146	3.7 (3.1 to 4.4)	1.00 [Reference]
GLP-1 RAs	5,505	30	9,580	3.1 (2.2 to 4.5)	0.83 (0.49 to 1.39)
Q3					
SGLT-2 inhibitors	18,254	68	31,781	4.3 (3.7 to 5.0)	1.00 [Reference]
GLP-1 RAs	6,201	44	10,669	4.1 (3.1 to 5.5)	0.93 (0.55 to 1.57)
Q4					
SGLT-2 inhibitors	21,877	101	37,833	5.1 (4.5 to 5.9)	1.00 [Reference]
GLP-1 RAs	7,203	55	12,173	4.5 (3.5 to 5.9)	0.85 (0.53 to 1.36)
Q5 (most deprived)					
SGLT-2 inhibitors	23,955	157	41,586	6.3 (5.6 to 7.0)	1.00 [Reference]
GLP-1 RAs	8,713	87	14,981	5.8 (4.7 to 7.2)	0.89 (0.62 to 1.28)

Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; Q, quintile; SGLT-2, sodium-glucose cotransporter-2

[a] Unknown socioeconomic status was included in the analysis, but not presented in the table.

[b] Per 1,000 person-years.

[c] The models were weighted using propensity score fine stratification.

Supplementary Table S15: Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with SGLT-2 Inhibitors; Interaction with Decile of Propensity Score

Exposure	Mean PS in decile	No. of patients	Events	Person-years	Weighted IR (95% CI) [a,b]	Weighted HR (95% CI) [b,c]
D1						
SGLT-2 inhibitors	0.08	43,941	124	72,070	1.7 (1.2 to 2.51)	1.00 [Reference]
GLP-1 RAs		3,233	15	4,386	3.4 (1.9 to 5.64)	1.87 (1.09 to 3.22)
D2						
SGLT-2 inhibitors	0.17	16,575	73	29,157	2.7 (1.9 to 3.6)	1.00 [Reference]
GLP-1 RAs		3,234	21	4,918	4.3 (2.6 to 6.5)	1.54 (0.94 to 2.50)
D3						
SGLT-2 inhibitors	0.22	10,898	54	19,611	2.8 (2.1 to 3.7)	1.00 [Reference]
GLP-1 RAs		3,234	11	5,071	2.2 (1.1 to 3.9)	0.74 (0.38 to 1.41)
D4						
SGLT-2 inhibitors	0.28	7,626	50	13,799	3.7 (2.8 to 4.7)	1.00 [Reference]
GLP-1 RAs		3,233	26	5,120	5.1 (3.3 to 7.4)	1.33 (0.83 to 2.14)
D5						
SGLT-2 inhibitors	0.34	5,662	33	10,582	3.1 (2.4 to 4.1)	1.00 [Reference]
GLP-1 RAs		3,234	15	5,466	2.7 (1.5 to 4.5)	0.85 (0.46 to 1.56)
D6						
SGLT-2 inhibitors	0.41	4,158	32	7,777	4.1 (3.2 to 5.1)	1.00 [Reference]
GLP-1 RAs		3,234	27	5,590	4.8 (3.2 to 7.0)	1.15 (0.69 to 1.92)

D7						
SGLT-2 inhibitors	0.49	3,147	30	6,205	4.9 (4.0 to 6.0)	1.00 [Reference]
GLP-1 RAs		3,233	25	5,737	4.4 (2.8 to 6.4)	0.85 (0.50 to 1.46)
D8						
SGLT-2 inhibitors	0.60	2,384	32	4,958	6.6 (5.5 to 7.8)	1.00 [Reference]
GLP-1 RAs		3,234	30	5,832	5.1 (3.5 to 7.3)	0.74 (0.45 to 1.22)
D9						
SGLT-2 inhibitors	0.75	1,317	12	2,953	4.17 (3.4 to 5.1)	1.00 [Reference]
GLP-1 RAs		3,234	35	6,589	5.31 (3.7 to 7.4)	1.22 (0.62 to 2.41)
D10						
SGLT-2 inhibitors	0.89	504	14	1,272	4.2 (3.4 to 5.1)	1.00 [Reference]
GLP-1 RAs		3,233	35	6,913	5.3 (3.7 to 7.4)	0.49 (0.26 to 0.92)

Abbreviations: CI, confidence interval; D, decile; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; PS, propensity score; SGLT-2, sodium-glucose cotransporter-2

[a] Per 1,000 person-years.

[b] The models were weighted using propensity score fine stratification.

Supplementary Table S16. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with SGLT-2 Inhibitors; Sensitivity Analyses

Exposure	No. of patients	Events	Person-years	Crude IR [a]	Weighted IR (95% CI) [a,b]	Crude HR (95% CI)	Weighted HR (95% CI) [b]
60-day grace period							
SGLT-2 inhibitors	96,212	415	151,439	2.7	4.7 (4.4 to 5.0)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	32,336	211	48,191	4.4	4.4 (3.8 to 5.0)	1.59 (1.34 to 1.87)	0.90 (0.71 to 1.12)
120-day grace period							
SGLT-2 inhibitors	96,212	479	177,508	2.7	4.5 (4.2 to 4.8)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	32,336	263	59,380	4.4	4.4 (3.9 to 5.0)	1.65 (1.42 to 1.91)	0.95 (0.77 to 1.17)
Intention-to-treat analysis [c]							
SGLT-2 inhibitors	96,212	285	88,831	3.2	5.5 (5.0 to 6.0)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	32,336	165	30,412	5.4	5.4 (4.6 to 6.3)	1.70 (1.40 to 2.05)	0.99 (0.77 to 1.29)
Multiple imputation							
SGLT-2 inhibitors	96,210	454	168,378	2.7	4.5 (4.2 to 4.8)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	32,337	240	55,620	4.3	4.3 (3.8 to 4.9)	1.60 (1.37 to 1.87)	0.92 (0.74 to 1.14)
Including diagnoses of the outcome captured in the CPRD database							
SGLT-2 inhibitors	96,212	494	168,341	2.9	5.0 (4.7 to 5.4)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	32,336	265	55,591	4.8	4.8 (4.2 to 5.4)	1.62 (1.40 to 1.88)	0.91 (0.74 to 1.12)

Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; SGLT-2, sodium-glucose cotransporter-2

[a] Per 1,000 person-years.

[b] The models were weighted using propensity score fine stratification.

[c] Patients were censored by the end of the first year.

Supplementary Table S17. Hazard Ratios and 95% CIs for Self-harm, Suicide Attempt, and Completed Suicide Comparing GLP-1 RAs with SGLT-2 Inhibitors; Inverse Probability of Censoring Weighting

Exposure	Events	Person-times	Crude IR [a]	Weighted IR (95% CI) [a,b]	Crude HR (95% CI)	Weighted HR (95% CI) [b]
SGLT-2 inhibitors	454	168,384	2.7	5.5 (5.2 to 5.9)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	240	55,620	4.3	5.0 (4.4 to 5.7)	1.60 (1.37 to 1.87)	0.91 (0.72 to 1.15)

Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; SGLT-2, sodium-glucose cotransporter-2

[a] Per 1,000 person-time intervals (90-day interval).

[b] The models were weighted using propensity score fine stratification and inverse probability of censoring weights.