Risk of hair loss associated with glucagon-like peptide-1 receptor agonists in adults with type 2 diabetes: target trial emulation

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ABSTRACT

OBJECTIVE

To examine the association between glucagon-like peptide-1 (GLP-1) receptor agonists and the risk of incident alopecia (hair loss) in adults with type 2 diabetes, compared with sodium-glucose cotransporter-2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors.

DESIGN

Target trial emulation.

SETTING

Electronic health records from Penn Medicine.

PARTICIPANTS

Adults (>18 years) with type 2 diabetes.

EXPOSURES

New initiation of GLP-1 receptor agonists, SGLT-2 inhibitors, or DPP-4 inhibitors between January 2019 and September 2024.

MAIN OUTCOME MEASURES

Outcomes of interest included incident alopecia and its subtypes, identified by using diagnostic codes. Stabilised inverse probability of treatment weighting was applied to balance baseline covariates between treatment groups, and Cox proportional hazards models were used to estimate hazard ratios with 95% confidence intervals. Multiple sensitivity (including negative control outcome calibration) and subgroup analyses were done to assess robustness.

RESULTS

This study included 12 004 GLP-1 receptor agonist initiators and 15 221 SGLT-2 inhibitor initiators in the GLP-1 receptor agonist versus SGLT-2 inhibitor comparison and 11 964 GLP-1 receptor agonist initiators and 11 238 DPP-4 inhibitor initiators in the GLP-1 receptor agonist versus DPP-4 inhibitor comparison. After stabilised inverse probability of treatment weighting adjustment, use of GLP-1 receptor agonists was associated with a higher risk of alopecia than use of SGLT-2 inhibitors (hazard ratio 1.37, 95% confidence interval 1.08 to 1.73) or DPP-4 inhibitors (1.68, 1.28 to 2.20). The associations were consistent across sensitivity and subgroup analyses, with attenuation after negative control outcome calibration. Subtype analyses indicated that the association was specific to non-scarring alopecia, with hazard ratios of 1.53 (1.18 to 1.97) and 1.72 (1.28 to 2.31) compared with SGLT-2 inhibitors and DPP-4 inhibitors, respectively.

CONCLUSIONS

Use of GLP-1 receptor agonists was associated with an increased risk of non-scarring alopecia in adults with type 2 diabetes. Although the absolute risk is low, awareness of this potential effect may help to inform treatment decisions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Hair loss (alopecia) has been reported in post-marketing surveillance as a possible adverse effect of glucagon-like peptide-1 (GLP-1) receptor agonists

Population based studies assessing the risk of alopecia associated with GLP-1 receptor agonists compared with sodium-glucose cotransporter-2 (SGLT-2) inhibitors or dipeptidyl peptidase-4 (DPP-4) inhibitors are lacking

WHAT THIS STUDY ADDS

GLP-1 receptor agonist use was associated with a higher risk of clinically recorded alopecia, particularly non-scarring alopecia, in patients with type 2 diabetes, compared with SGLT-2 and DPP-4 inhibitors

These findings may inform shared decision making when considering GLP-1 receptor agonist therapy and highlight the need for further evaluation of dermatological outcomes in future studies

Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists are increasingly prescribed for the management of type 2 diabetes and, more recently, for obesity treatment in populations without diabetes.[1-3] Recent postmarketing reports have suggested a possible association between GLP-1 receptor agonist use and alopecia (hair loss).[4] Case reports and analyses of the US Food and Drug Administration (FDA)'s Adverse Event Reporting System have described occurrences of hair loss following initiation of a GLP-1 receptor agonist, particularly semaglutide and tirzepatide.[5-7] In response, the FDA has indicated that it is evaluating this potential safety signal.[8] Although hair loss does not typically result in physical harm, it may have significant psychosocial consequences, affecting self-esteem, quality of life, and adherence to treatment.[9]

Weight loss and changes in nutritional status, common consequences of GLP-1 receptor agonist therapy,[10 11] are established risk factors for telogen effluvium, a common and typically transient form of non-scarring hair loss, providing a plausible biological mechanism for this association.[12 13] To date, no large scale, population based studies have systematically evaluated the risk of alopecia associated with GLP-1 receptor agonists. Randomised controlled trials have not routinely captured alopecia as an adverse event, and previous observational studies have been limited by small sample sizes, lack of appropriate comparators, and insufficient adjustment for confounding.[14] Given the expanding clinical use of GLP-1 receptor agonists, particularly in younger and non-diabetic populations, timely evidence is needed to inform clinical practice and regulatory decisions.

In this study, we emulated a target trial by using electronic health record data from a large, multisite academic health system to examine the association between GLP-1 receptor agonist initiation and the incidence of alopecia, compared with two active comparator drug classes: sodium-glucose cotransporter-2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors. By leveraging large, real world datasets and a robust analytical framework, this study aims to provide timely, clinically relevant evidence on the potential hair related safety profile of GLP-1 receptor agonists.

Methods

Study design and data sources

We conducted a target trial emulation study using electronic health record data from the University of Pennsylvania Health System (Penn Medicine) between January 2019 and September 2024. Our study followed the target trial emulation framework, incorporating eligibility criteria, treatment strategies, assignment procedures, follow-up period, outcome, causal contrasts, and analysis plan aligned with an ideal randomised controlled trial, which we then emulated by using observational data (supplementary table S1; supplementary text).[15] Reporting followed the electronic health record (TARGET) guideline for target trial emulation studies.[16]

Penn Medicine's electronic health record repository integrates longitudinal, multisite, real world clinical data from the Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, Pennsylvania Hospital, Chester County Hospital, and Penn Medicine Princeton Medical Center, as well as multiple outpatient practices and affiliated healthcare networks. This dataset encompasses more than 6.5 million unique patients and more than 50 million clinical encounters across the greater Philadelphia metropolitan area, central Pennsylvania, Delaware, and southern New Jersey. It contains comprehensive information on patients' demographics, diagnoses, medications, laboratory results, procedures, and clinical outcomes, making it a robust resource for assessing the real world effectiveness and safety of medical interventions.

Study population

We identified adults (aged >18 years) with a diagnosis of type 2 diabetes, defined by using ICD-10 (international classification of diseases, 10th revision) codes, who newly initiated a GLP-1 receptor agonist, SGLT-2 inhibitor, or DPP-4 inhibitor during the study period. We required individuals to have no prescriptions for the index drug class in the 12 months before their first eligible prescription (defined as the index date). The ICD codes are listed in supplementary table S2. Patients were excluded if they had a diagnosis of alopecia, type 1 diabetes, end stage renal disease/dialysis, or use of a competing glucose lowering drug class in the year before the index date.

Exposure and comparator definition

We defined exposure as initiation of a GLP-1 receptor agonist (exenatide, liraglutide, dulaglutide, semaglutide, lixisenatide, or tirzepatide). Comparator groups were new users of either SGLT-2 inhibitors (for example, canagliflozin, dapagliflozin, empagliflozin) or DPP-4 inhibitors (for example, sitagliptin, saxagliptin, linagliptin) (supplementary table S2). We selected SGLT-2 inhibitors and DPP-4 inhibitors as active comparators because they represent commonly prescribed, guideline recommended alternatives to GLP-1 receptor agonists for the management of type 2 diabetes in routine clinical practice.[17] These drug classes have overlapping indications with GLP-1 receptor agonists, were typically initiated at similar stages of the treatment pathway during the study period, and are prescribed to broadly comparable patient populations, thereby reducing confounding by indication. In addition, the use of active comparators with similar healthcare seeking behaviours, clinical monitoring, and treatment intensity helps to minimise bias related to differences in disease severity and healthcare use that may arise when using non-user or general population comparators.[18]

Outcome assessment and follow-up

The primary outcome was incident alopecia, identified by using ICD-10 diagnostic codes recorded in the electronic health record system (supplementary table S2).[19] In a previous US based validation study, a claims based algorithm relying on a single ICD-10-CM code for any alopecia diagnosis showed high validity, with a positive predictive value of 95.3%.[19] We defined an incident case of alopecia as the first occurrence of an alopecia diagnosis documented after the initiation of the study drug. Secondary outcomes included specific subtypes of alopecia: alopecia areata, androgenic alopecia, other non-scarring alopecia (including telogen effluvium, anagen effluvium, alopecia mucinosa, and other non-scarring hair loss), and cicatricial alopecia (scarring hair loss), identified by using corresponding ICD-10 codes (supplementary table S2).

We followed patients from the index date until the earliest occurrence of alopecia, death, five years of follow-up, or the end of the study period. We used an intention-to-treat approach, whereby we analysed patients according to their initial treatment group regardless of subsequent treatment modifications.[20] This strategy reflects real world treatment effectiveness and maintains comparability between groups.[21]

Baseline covariates

Baseline covariates were measured during the 12-month before the index date to control for potential confounding, identified using a directed acyclic graphs, which are shown in supplementary figure S1. The complete list of baseline covariates is provided in table 1 and table 2 and included demographics (for example, age, sex, race/ethnicity), socioeconomic factors and insurance, healthcare utilisation, comorbidities (for

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Table 1 | Baseline characteristics of patients included in GLP-1RA *v* SGLT2i and GLP-1RA *v* DPP4i cohorts, in adults with type 2 diabetes (part 1). Values are numbers (percentages) unless stated otherwise

	GLP-1RA v SGLT2i				GLP-1RA v DPP4i			
	GlLP-1RA (n=12 004)	SGLT-2i (n=15 221)	$SMD_{before\ sIPTW}$	$SMD_{after\ sIPTW}$	GLP-1RA (n=11 964)	DPP-4i (n=11 233)	$SMD_{before\ sIPTW}$	$SMD_{after\ sIPTW}$
Demographics/healthcare use								
Mean (SD) age, years	58.1(12.7)	64.5 (12.0)	0.523	0.009	58.0 (12.7)	66.9 (13.2)	0.688	0.007
Female sex	6662 (55.5)	5801 (38.1)	0.354	0.006	6636 (55.5)	5399 (48.1)	0.149	0.012
Race/ethnicity:								
Hispanic	609 (5.1)	776 (5.1)	0.243	0.005	608 (5.1)	642 (5.7)	0.333	0.018
Non-Hispanic white	5422 (45.2)	7737 (50.8)			5412 (45.2)	5783 (51.5)		
Non-Hispanic black	4701 (39.2)	4349 (28.6)			4672 (39.1)	2802 (24.9)		
Other/unknown	1272 (10.6)	2359 (15.5)			1272 (10.6)	2006 (17.9)		
Health insurance*								
Commercial	5251 (43.7)	4952 (32.5)	0.367	0.012	5252 (43.9)	3131 (27.9)	0.483	0.012
Medicare	3760 (31.3)	6201 (40.7)			3725 (31.1)	5677 (50.5)		
Medicaid	1766 (14.7)	1334 (8.8)			1761 (14.7)	853 (7.6)		
Other/unknown	1227 (10.2)	2734 (18.0)			1226 (10.2)	1572 (14.0)		
Entry year:								
2019	2704 (22.5)	1644 (10.8)	0.428	0.038	2664 (22.3)	3493 (31.1)	0.369	0.03
2020	1684 (14.0)	1559 (10.2)			1684 (14.1)	2119 (18.9)		
2021	1170 (9.7)	1496 (9.8)			1170 (9.8)	1249 (11.1)		
2022	1917 (16.0)	2780 (18.3)			1917 (16.0)	1899 (16.9)		
2023	2786 (23.2)	3592 (23.6)			2786 (23.3)	1407 (12.5)		
2024	1743 (14.5)	4150 (27.3)			1743 (14.6)	1066 (9.5)		
Charlson Comorbidity Index:								
≤1	2507 (20.9)	2799 (18.4)	0.277	0.011	2491 (20.8)	3666 (32.6)	0.383	0.021
2-5	5645 (47.0)	5534 (36.4)			5652 (47.2)	3336 (29.7)		
≥6	3852 (32.1)	6888 (45.3)			3821 (31.9)	4231 (37.7)		
Emergency visits (≥1)	1555 (13.0)	1650 (10.8)	0.065	0.009	1548 (12.9)	1179 (10.5)	0.076	0.013
Inpatient visits (≥1)	1549 (12.9)	3027 (19.9)	0.189	0.01	1540 (12.9)	2520 (22.4)	0.253	0.005
Outpatient visits:								
0	759 (6.3)	1234 (8.1)	0.157	0.011	755 (6.3)	1296 (11.5)	0.296	0.007
1-20	4619 (38.5)	6758 (44.4)			4616 (38.6)	5277 (47.0)		
>20	6626 (55.2)	7229 (47.5)			6593 (55.1)	4660 (41.5)		
Socioeconomic/psychosocial factors	179 (1.5)	277 (1.8)	0.026	0.002	180 (1.5)	181 (1.6)	0.009	0.007
Comorbidities								
Diabetic nephropathy	1131 (9.4)	2593 (17.0)	0.226	0.015	1123 (9.4)	1529 (13.6)	0.133	0.009
Diabetic retinopathy	589 (4.9)	762 (5.0)	0.005	0.01	586 (4.9)	410 (3.6)	0.062	0.019
Diabetic neuropathy	1073 (8.9)	1526 (10.0)	0.037	0.017	1069 (8.9)	962 (8.6)	0.013	0.006
Peripheral vascular disease	413 (3.4)	921 (6.1)	0.123	0.024	414 (3.5)	479 (4.3)	0.042	0.013
Other specified complications	4597 (38.3)	5483 (36.0)	0.047	0.016	4572 (38.2)	3723 (33.1)	0.106	0.004
Other unspecified complications	866 (7.2)	803 (5.3)	0.08	0.006	853 (7.1)	544 (4.8)	0.097	0.008
Coronary artery disease	1559 (13.0)	3801 (25.0)	0.309	0.011	1550 (13.0)	1972 (17.6)	0.128	0.009
Cardiomyopathy	467 (3.9)	2192 (14.4)	0.371	0.014	468 (3.9)	582 (5.2)	0.061	0.005
Acute myocardial infarction	226 (1.9)	864 (5.7)	0.2	0.009	225 (1.9)	298 (2.7)	0.052	0.001
Arrhythmias	1277 (10.6)	3348 (22.0)	0.311	0.005	1272 (10.6)	1892 (16.8)	0.181	0.016
Cerebrovascular disease	587 (4.9)	1194 (7.8)	0.121	0.003	581 (4.9)	923 (8.2)	0.136	0.016
Hypertension	7171 (59.7)	9784 (64.3)	0.094	0.001	7130 (59.6)	6595 (58.7)	0.018	0.006
Lipid disorders	6205 (51.7)	8986 (59.0)	0.148	0.008	6179 (51.6)	5913 (52.6)	0.02	0.005
Alcohol related disorders	143 (1.2)	269 (1.8)	0.048	0.002	141 (1.2)	172 (1.5)	0.031	0.004
Tobacco related disorders	862 (7.2)	1229 (8.1)	0.034	0.008	853 (7.1)	769 (6.8)	0.011	0.007
Anxiety disorders	1403 (11.7)	1500 (9.9)	0.059	0.016	1404 (11.7)	1039 (9.2)	0.081	0.005
Asthma	1230 (10.2)	1084 (7.1)	0.111	<0.001	1226 (10.2)	744 (6.6)	0.131	0.013
Biliary tract disease	221 (1.8)	363 (2.4)	0.038	0.006	217 (1.8)	260 (2.3)	0.035	0.005
Bronchitis	232 (1.9)	298 (2.0)	0.002	0.008	234 (2.0)	225 (2.0)	0.003	0.005
Chronic kidney disease	1108 (9.2)	2746 (18.0)	0.259	0.02	1098 (9.2)	1746 (15.5)	0.194	0.004
Chronic obstructive pulmonary disease	649 (5.4)	1273 (8.4)	0.117	0.001	646 (5.4)	759 (6.8)	0.057	0.006
Covid-19	491 (4.1)	654 (4.3)	0.01	0.009	490 (4.1)	377 (3.4)	0.039	0.006
Cognitive impairment	377 (3.1)	644 (4.2)	0.058	0.008	372 (3.1)	646 (5.8)	0.129	0.011
Fractures	287 (2.4)	401 (2.6)	0.016	0.006	286 (2.4)	355 (3.2)	0.047	0.015
Glaucoma	467 (3.9)	604 (4.0)	0.004	0.003	468 (3.9)	386 (3.4)	0.025	0.008
Obesity	4815 (40.1)	3865 (25.4)	0.318	0.009	4794 (40.1)	2136 (19.0)	0.474	0.003
Osteoarthritis	1497 (12.5)	1647 (10.8)	0.051	0.002	1481 (12.4)	1230 (10.9)	0.045	0.004
Pancreatic disorders	122 (1.0)	286 (1.9)	0.072	0.011	121 (1.0)	166 (1.5)	0.042	0.005
Pneumonia	282 (2.3)	570 (3.7)	0.081	0.004	282 (2.4)	460 (4.1)	0.098	0.006
Skin cancers	148 (1.2)	229 (1.5)	0.023	0.008	150 (1.3)	200 (1.8)	0.043	0.013
Thyroid disorders	611 (5.1)	573 (3.8)	0.064	0.008	607 (5.1)	422 (3.8)	0.064	0.002
Malnutrition	119 (1.0)	394 (2.6)	0.121	0.008	119 (1.0)	398 (3.5)	0.172	0.012

(Continued)

Table 1 | Continued

	GLP-1RA v SGLT2i				GLP-1RA v DPP4i			
	GlLP-1RA (n=12 004)	SGLT-2i (n=15 221)	$SMD_{before\ sIPTW}$	$SMD_{after\ sIPTW}$	GLP-1RA (n=11 964)	DPP-4i (n=11 233)	$SMD_{before\ sIPTW}$	$SMD_{after\ sIPTW}$
Menstrual disorders	221 (1.8)	78 (0.5)	0.123	0.005	223 (1.9)	49 (0.4)	0.134	0.033
Thrombophlebitis/thromboembolism	468 (3.9)	923 (6.1)	0.1	0.014	468 (3.9)	483 (4.3)	0.02	0.009
Polycystic ovary syndrome	193 (1.6)	58 (0.4)	0.124	0.014	194 (1.6)	28 (0.2)	0.143	0.001
Autoimmune diseases	283 (2.4)	351 (2.3)	0.003	0.009	282 (2.4)	311 (2.8)	0.026	0.008

DPP-4i=dipeptidyl peptidase-4 inhibitor; GLP-1RA=glucagon-like peptide-1 receptor agonist; SD=standard deviation; SGLT-2i=sodium-glucose cotransporter-2 inhibitor; sIPTW=stabilised inverse probability treatment weighting; SMD=standardised mean difference.
*"Commercial" insurance refers to employer sponsored or privately purchased plans. "Medicare" is a federal programme primarily for adults aged ≥65 years and certain younger individuals with disabilities. "Medicaid" is a joint federal-state programme for individuals with limited income, with eligibility and benefits varying by state. "Other/unknown" includes less common categories or missing data.

example, cerebrovascular disease, coronary artery disease, hypertension, dyslipidaemia, chronic kidney disease, and thyroid disorders), medication use (for example, antihypertensives, other glucose lowering drugs, antidepressants, and hormones), and laboratory and vital values (for example, baseline glycated haemoglobin (HbA_{1c}) levels, body mass index, blood pressure, and estimated glomerular filtration rate. We accounted for missing data in laboratory and vital variables by using single imputation, incorporating all baseline covariates in the imputation model.[22]

Statistical analysis

We used descriptive statistics to summarise baseline characteristics: means and standard deviations for continuous variables and counts and proportions for categorical variables. To adjust for confounding and improve balance between treatment groups, we applied stabilised inverse probability of treatment weighting (sIPTW) based on propensity scores estimated via logistic regression, including all relevant baseline covariates.[23] We assessed covariate balance before and after weighting by using standardised mean differences, with a standardised mean difference <0.1 indicating adequate balance.[24] We used Love plots to visually assess balance across groups.

To evaluate the risk of alopecia associated with GLP-1 receptor agonists compared with SGLT-2 inhibitors or DPP-4 inhibitors, we fitted Cox proportional hazards regression models before and after sIPTW. We used robust variance estimators to account for weighting and calculated hazard ratios with 95% confidence intervals by using robust standard errors. We used Schoenfeld residuals to evaluate the proportional hazards assumption. We generated sIPTW adjusted Kaplan-Meier curves to visualise the cumulative incidence of alopecia across the groups.

We evaluated pre-specified subgroups for effect modification by the following key variables: age (<65 *v* ≥65 years); sex; race and ethnicity (Hispanic *v* non-Hispanic white *v* non-Hispanic black *v* others); obesity; coronary artery disease; chronic kidney disease; hypertension; entry year (2019-22 *v* 2023-24, given the potential safety problem raised by the US FDA in 2023[8]); insulin use; metformin use; molecular structure of GLP-1 receptor agonist (semaglutide *v* tirzepatide *v* liraglutide *v* dulaglutide). To ensure adequate covariate balance within each subgroup, we refitted sIPTW models separately within each stratum.

We did several sensitivity analyses to assess the robustness of primary findings: applying sIPTW with a truncation at 1% and 99%; conducting 1:1 propensity score matching using nearest neighbour matching with a caliper of 0.1 of the standard deviation of the logit of the propensity score; applying a 30 or 60 day lag period by excluding individuals with a diagnosis of alopecia within the first 30 or 60 days after the index date to minimise potential reverse causation and protopathic bias; following a per protocol approach, in which patients were followed from the index date until the earliest of the following events - last prescription date, initiation of a competing medication, first occurrence of alopecia, death, five years of follow-up, or the end of the study period; requiring at least two diagnosis codes recorded on separate encounters to define the outcome, to reduce misclassification and improve the specificity of outcome ascertainment; and applying negative control outcome calibration to reduce potential residual confounding and systematic biases, using a list of 30 negative control outcomes with no plausible causal relations to exposure (supplementary table S3).[25-27] We derived an empirical null distribution from the negative control outcome effect estimates obtained using the same analytical framework as the primary analysis and used it to generate calibrated effect estimates and confidence intervals. Moreover, to assess the robustness of our findings to potential unmeasured confounding, we did an E value analysis for the primary outcome. The E value indicates the minimum strength of association that an unmeasured confounder would need to have with both GLP-1 receptor agonist use and alopecia, conditional on measured covariates, to fully explain the observed association.[28 29] We used R (version 4.2.2) for statistical analyses, with two sided P values <0.05 considered statistically significant.

Patient and public involvement

No patients were involved in setting the research question, developing the study design, defining the outcome measures, interpreting the data, or reporting the findings because this was a retrospective observational study using de-identified electronic health record data without direct patient contact.

Table 2 | Baseline characteristics of patients included in GLP-1RA *v* SGLT2i and GLP-1RA *v* DPP4i cohorts, in adults with type 2 diabetes (part 2). Values are numbers (percentages) unless stated otherwise

	GLP-1RA v SGLT2i				GLP-1RA v DPP4i			
	GlLP-1RA (n=12 004)	SGLT-2i (n=15 221)	$SMD_{before\ sIPTW}$	$SMD_{after\ sIPTW}$	GLP-1RA (n=11 964)	DPP-4i (n=11 233)	$SMD_{before\ sIPTW}$	$SMD_{after\ sIPTW}$
Medications								
Insulin	3995 (33.3)	5265 (34.6)	0.028	0.01	3969 (33.2)	4365 (38.9)	0.119	0.011
Metformin	7117 (59.3)	8540 (56.1)	0.064	0.008	7082 (59.2)	6966 (62.0)	0.058	0.002
Sulfonylureas	1854 (15.4)	2939 (19.3)	0.102	0.021	1813 (15.2)	3076 (27.4)	0.302	0.011
DPP-4i/SGLT-2i	121 (1.0)	109 (0.7)	0.032	0.009	81 (0.7)	51 (0.5)	0.03	0.013
Thiazolidinediones	277 (2.3)	464 (3.0)	0.046	0.003	269 (2.2)	402 (3.6)	0.079	0.007
α glucosidase inhibitors	18 (0.1)	36 (0.2)	0.02	0.002	16 (0.1)	40 (0.4)	0.045	0.002
ARB/ACEi	6523 (54.3)	9471 (62.2)	0.16	0.004	6491 (54.3)	6495 (57.8)	0.072	0.003
Calcium channel blockers	3717 (31.0)	5190 (34.1)	0.067	0.006	3686 (30.8)	3898 (34.7)	0.083	0.01
Diuretics	5610 (46.7)	8254 (54.2)	0.15	0.004	5581 (46.6)	5711 (50.8)	0.084	0.001
Lipid lowering drugs	7828 (65.2)	11 305 (74.3)	0.198	0.002	7781 (65.0)	7931 (70.6)	0.119	0.004
Corticosteroids	2430 (20.2)	2835 (18.6)	0.041	0.008	2408 (20.1)	2148 (19.1)	0.025	0.01
NSAIDs	3504 (29.2)	3251 (21.4)	0.181	0.009	3484 (29.1)	2646 (23.6)	0.127	<0.001
Antidepressants	3386 (28.2)	3440 (22.6)	0.129	0.003	3367 (28.1)	2623 (23.4)	0.11	0.006
Antipsychotics	922 (7.7)	1248 (8.2)	0.019	0.012	921 (7.7)	1072 (9.5)	0.066	0.002
Antidementia drugs	73 (0.6)	156 (1.0)	0.046	0.021	73 (0.6)	243 (2.2)	0.133	0.014
Anticoagulants	845 (7.0)	2222 (14.6)	0.245	0.009	842 (7.0)	1229 (10.9)	0.137	0.005
Antiplatelet agents	2822 (23.5)	5308 (34.9)	0.252	0.013	2803 (23.4)	3839 (34.2)	0.239	0.002
Proton pump inhibitors	3103 (25.8)	4220 (27.7)	0.042	0.002	3085 (25.8)	3273 (29.1)	0.075	<0.001
Opioids	3165 (26.4)	4519 (29.7)	0.074	0.011	3150 (26.3)	3502 (31.2)	0.107	<0.001
Other anti-obesity drug	821 (6.8)	646 (4.2)	0.114	0.002	819 (6.8)	384 (3.4)	0.156	0.003
Testosterone therapy	126 (1.0)	120 (0.8)	0.027	0.004	123 (1.0)	84 (0.7)	0.03	0.009
Hormonal contraceptives	338 (2.8)	154 (1.0)	0.132	0.011	339 (2.8)	134 (1.2)	0.117	0.015
Anti-androgens	19 (0.2)	23 (0.2)	0.002	0.002	18 (0.2)	32 (0.3)	0.029	0.009
Thyroid hormones	1196 (10.0)	1602 (10.5)	0.019	0.004	1196 (10.0)	1436 (12.8)	0.088	0.002
Laboratory and vital values								
Mean (SD) HbA1c, %	8.0 (1.9)	7.9 (1.8)	0.031	0.021	8.0 (1.9)	8.0 (1.7)	0.002	0.02
Mean (SD) body mass index	36.2 (7.5)	32.3 (6.9)	0.539	0.008	36.2 (7.5)	31.3 (6.7)	0.693	0.014
Mean (SD) systolic blood pressure, mm Hg	131.3 (16.1)	130.5 (17.2)	0.054	0.003	131.3 (16.2)	132.2 (17.5)	0.05	0.002
Mean (SD) diastolic blood pressure, mm Hg	78.5 (9.9)	76.5 (10.1)	0.204	0.02	78.6 (9.9)	76.1 (10.4)	0.242	0.004
Mean (SD) eGFR, mL/min/1.73 m^2	85.2 (28.4)	76.6 (29.0)	0.298	0.008	85.3 (28.4)	73.8 (29.2)	0.399	0.004

ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin-receptor blocker; DPP-4i=dipeptidyl peptidase-4 inhibitor; eGFR=estimated glomerular filtration rate; GLP-1RA=glucagon-like peptide-1 receptor agonist; NSAID=non-steroidal anti-inflammatory drug; SD=standard deviation; SGLT-2i=sodium-glucose cotransporter-2 inhibitor; sIPTW=stabilised inverse probability treatment weighting; SMD=standardised mean difference.

Results

Baseline characteristics

The flowchart of patient selection is presented in supplementary figure S2. On the basis of the inclusion and exclusion criteria, a total of 12 004 patients using GLP-1 receptor agonists and 15 221 using SGLT-2 inhibitors were included in the GLP-1 receptor agonist versus SGLT-2 inhibitor cohort; 11 964 GLP-1 receptor agonist users and 11 233 DPP-4 inhibitor users were included in the GLP-1 receptor agonist versus DPP-4 inhibitor cohort. Table 1 and table 2 show the baseline characteristics. Before sIPTW, in the GLP-1 receptor agonist versus SGLT-2 inhibitor cohort, GLP-1 receptor agonist users were younger (mean age 58.1 *v* 64.5 years), had a higher body mass index (36.2 *v* 32.3), and had a lower prevalence of cerebrovascular disease, coronary artery disease, and chronic kidney disease than SGLT-2 inhibitor users. Similarly, in the GLP-1 receptor agonist versus DPP-4 inhibitor cohort, GLP-1 receptor agonist users were younger (mean age 58.0 *v* 66.9 years) and had a higher body mass index (36.2 *v* 31.3) than DPP-4 inhibitor users. After applying sIPTW, the distributions of propensity scores showed good overlap between treatment groups (supplementary figure S3) and baseline covariate balance improved substantially, with all standardised mean differences below 0.1 (table 1, table 2, and supplementary figure S4). The proportional hazards assumptions were satisfied on the basis of Schoenfeld residuals (supplementary table S4). The mean time to onset of alopecia was 1.71 (standard deviation (SD) 1.33) years for GLP-1 receptor agonist users and 1.67 (1.34) years for SGLT-2 inhibitor users; corresponding values in the GLP-1 receptor agonist versus DPP-4 inhibitor comparison were 1.81 (1.34) and 2.09 (1.43) years, respectively (supplementary figure S5). Weighted density estimates showed that alopecia events were concentrated in the first year after treatment initiation, peaking just before 12 months. Healthcare use during follow-up was similar across treatment groups (supplementary table S5).

Primary analyses

Table 3 shows the results from the primary analyses. In the GLP-1 receptor agonist versus SGLT-2 inhibitor cohort, the mean follow-up was 2.66 (SD 1.70) years for GLP-1 receptor agonist users and 2.03 (1.59) years for SGLT-2 inhibitor users. The crude incidence rate

of alopecia was 8.65 versus 4.25 per 1000 person years, yielding a hazard ratio of 2.06 (95% confidence interval (CI) 1.67 to 2.54). After sIPTW adjustment, the incidence rates were 6.91 versus 5.04 and the adjusted hazard ratio was 1.37 (1.08 to 1.73). In the GLP-1 receptor agonist versus DPP-4 inhibitor cohort, follow-up was 2.65 (SD 1.70) years for GLP-1 receptor agonist users and 3.10 (1.68) years for DPP-4 inhibitor users. The crude incidence rates were 8.64 versus 2.96, with a hazard ratio of 2.91 (95% CI 2.32 to 3.65). After sIPTW adjustment, the incidence rates were 6.53 versus 3.89 and the hazard ratio was 1.68 (1.28 to 2.20). Figure 1 shows the Kaplan-Meier curve illustrating the cumulative incidence of alopecia in the two groups.

Subgroup and sensitivity analyses

Subgroup analyses stratified by age, sex, race/ethnicity, obesity status, coronary artery disease, chronic kidney disease, hypertension, entry year, insulin use, metformin use, and type of GLP-1 receptor agonist showed generally consistent associations across strata (fig 2; fig 3). We observed evidence of effect modification for metformin use in the GLP-1 receptor agonist versus SGLT-2 inhibitor comparison (P=0.02) and for race/ethnicity in the GLP-1 receptor agonist versus DPP-4 inhibitor comparison (P=0.03).

Sensitivity analyses supported the robustness of the primary findings (fig 4; fig 5). These included sIPTW with a truncation at 1% and 99%, 1:1 propensity score matching, implementation of a 30 or 60 day lag period, requiring at least two diagnosis codes on separate records, per protocol analysis, and negative control outcome calibration. The empirical null distribution of negative control outcomes, with their hazard ratios and corresponding standard errors, is presented in supplementary figure S6. The observed associations for the SGLT-2 inhibitor and DPP-4 inhibitor comparisons yielded E values of 2.08 and 2.75, respectively, and the lower bounds of the 95% confidence intervals corresponded to E values of 1.37 and 1.88, indicating moderate robustness to unmeasured confounding.

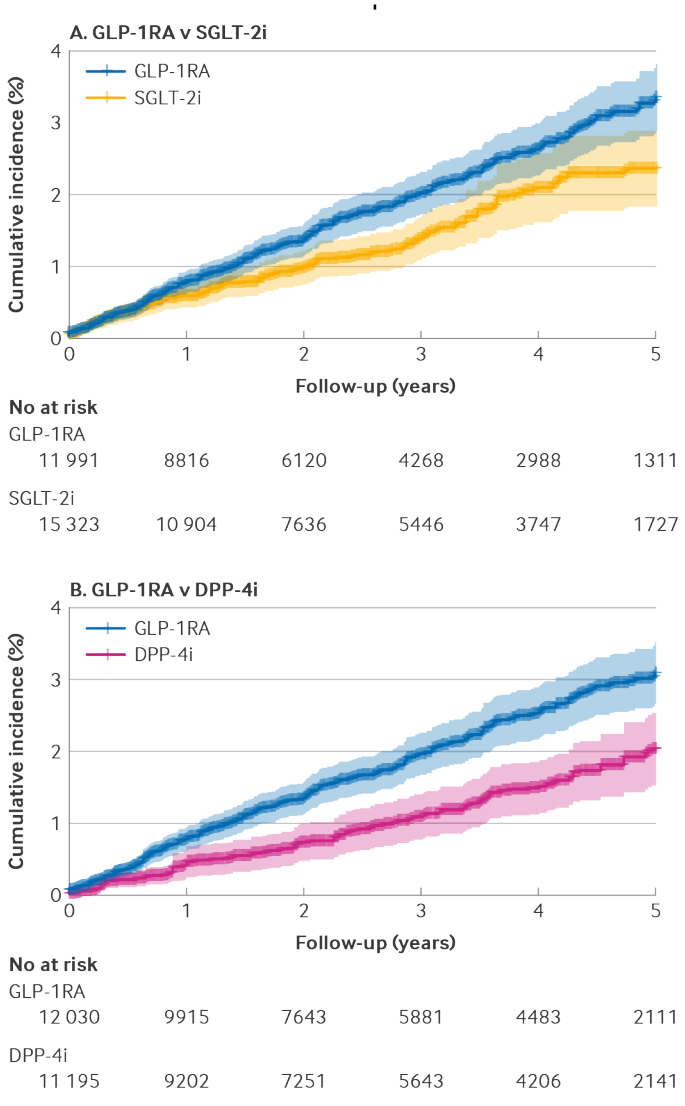

Fig 1 | Cumulative incidence of alopecia in stabilised inverse probability of treatment weight adjusted glucagon-like peptide-1 receptor agonist (GLP-1RA) versus sodium-glucose cotransporter-2 inhibitor (SGLT-2i) cohort (A) and GLP-1RA versus dipeptidyl peptidase-4 inhibitor (DPP-4i) (B), in adults with type 2 diabetes

Secondary outcomes

Table 4 and supplementary figure S7 show subtype specific outcomes of alopecia. We observed a significantly increased risk associated with use of GLP-1 receptor agonists for other non-scarring alopecia, compared with use of SGLT-2 inhibitors (hazard ratio 1.53, 95% CI 1.18 to 1.97) and DPP-4 inhibitors (1.72, 1.28 to 2.31). GLP-1 receptor agonist use was also associated with an increased risk of cicatricial alopecia compared with DPP-4 inhibitor use (hazard ratio 3.83, 1.55 to 9.46) but not compared with SGLT-2 inhibitor use (1.10, 0.56 to 2.16).

Discussion

In this large scale, population based target trial emulation, initiation of GLP-1 receptor agonists was associated with an increased risk of incident alopecia in adults with type 2 diabetes, particularly non-scarring alopecia, compared with SGLT-2 inhibitors and DPP-4 inhibitors. These associations were consistent across subgroup and sensitivity analyses, supporting the robustness of the findings. Our findings extend previous anecdotal safety signals and provide more systematic evidence to inform clinical awareness of this potential adverse effect. In addition, these results highlight the need for further research to elucidate potential mechanistic links between GLP-1 receptor agonist therapy, weight loss, and hair loss, and to identify patient level risk factors that may increase susceptibility to hair loss.

Comparison with other studies

Our findings align with and extend previous observations suggesting a possible association between GLP-1 receptor agonist use and alopecia.[5-7] Pharmacovigilance using the US FDA's Adverse Event Reporting System reported increased reporting odds

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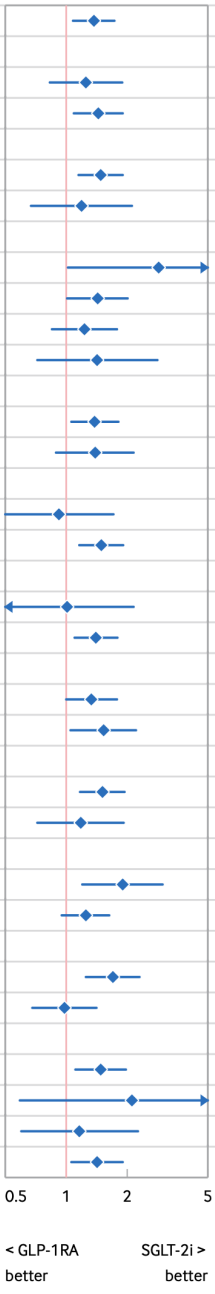
Subgroup analysis: GLP-1RAs versus SGLT-2is

Association between GLP-1RAs and risk of alopecia compared with SGLT-2is in adults with type 2 diabetes

Hazard ratios (HRs) and 95% confidence intervals (CIs) are shown for each subgroup, with P values for interaction assessing heterogeneity of treatment effect across subgroups. HR>1 indicates higher risk of alopecia with GLP-1RA use relative to comparator

Subgroup	Number of events/patients (GLP-1RA)	Number of events/patients (SGLT-2i)	P for interaction	HR (95% CI)
Overall	198/11 991	182/15 323		1.37 (1.08 to 1.73)
Age			0.58	
≥ 65 yrs	41/3672	67/7755		1.25 (0.83 to 1.89)
< 65 yrs	168/8286	106/7516		1.44 (1.09 to 1.90)
Sex			0.49	
Female	208/6654	124/5843		1.48 (1.15 to 1.90)
Male	21/5302	31/9473		1.19 (0.67 to 2.11)
Race/ethnicity			0.51	
Hispanics	14/604	6/780		2.86 (1.02 to 8.07)
NHW	77/5358	78/7802		1.43 (1.01 to 2.01)
NHB	94/4682	73/4440		1.23 (0.85 to 1.78)
Others	15/1275	19/2366		1.42 (0.72 to 2.82)
Obesity			0.98	
Yes	177/9430	122/8860		1.38 (1.06 to 1.81)
No	30/2547	52/6407		1.39 (0.89 to 2.15)
Coronary artery disease			0.15	
Yes	14/1484	38/3852		0.92 (0.50 to 1.71)
No	191/10 429	142/11 519		1.49 (1.16 to 1.91)
Chronic kideny disease			0.42	
Yes	11/1084	26/2750		1.01 (0.47 to 2.15)
No	191/10 840	157/12 569		1.40 (1.10 to 1.79)
Hypertension			0.56	
Yes	117/7092	121/9874		1.33 (1.00 to 1.78)
No	78/4819	58/5483		1.53 (1.05 to 2.21)
Entry year			0.38	
2023-2024	186/7464	124/7518		1.51 (1.17 to 1.94)
2019-2022	28/4737	38/7698		1.18 (0.72 to 1.92)
Insulin use			0.12	
Yes	53/3888	37/5333		1.90 (1.20 to 2.99)
No	145/8018	146/10 009		1.25 (0.95 to 1.63)
Metformin use			0.02	
Yes	137/7077	97/8595		1.70 (1.25 to 2.30)
No	61/4842	86/6759		0.98 (0.68 to 1.41)
Type of GLP-1RA			0.85	
Semaglutide	79/5032	154/15 211		1.48 (1.11 to 1.97)
Tirzepatide	5/622	130/15 230		2.11 (0.59 to 7.51)
Liraglutide	17/1624	147/15 203		1.16 (0.60 to 2.26)
Dulaglutide	73/4642	159/15 294		1.42 (1.06 to 1.90)



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GLP-1RA=glucagon-like peptide-1 receptor agonist; NHB=non-Hispanic black; NHW=non-Hispanic white; SGLT-2i=sodium-glucose cotransporter-2 inhibitor

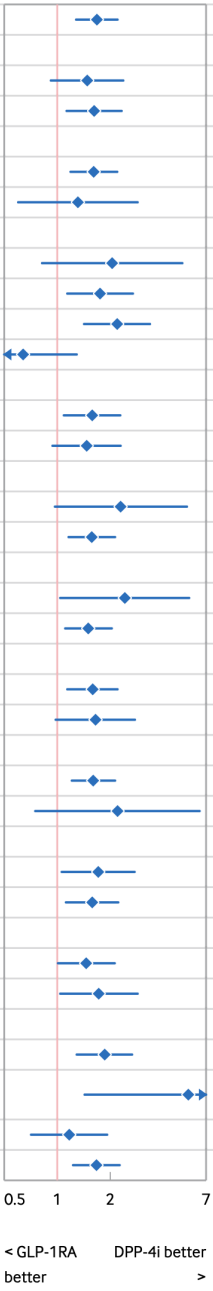
Fig 2 | Subgroup analysis of association between glucagon-like peptide-1 receptor agonists and risk of alopecia compared with sodium-glucose cotransporter-2 inhibitors. An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/29535058/

Subgroup analysis: GLP-1RAs versus DPP-4is

Association between GLP-1RAs and risk of alopecia compared with DPP-4is in adults with type 2 diabetes

Hazard ratios (HRs) and 95% confidence intervals (CIs) are shown for each subgroup, with P values for interaction assessing heterogeneity of treatment effect across subgroups. HR>1 indicates higher risk of alopecia with GLP-1RA use relative to comparator

Subgroup	Number of events/patients (GLP-1RA)	Number of events/patients (DPP-4i)	P for interaction	HR (95% CI)
Overall	229/12 030	128/11 195		1.68 (1.28 to 2.20)
Age			0.77	
≥ 65 yrs	45/3779	52/6516		1.48 (0.92 to 2.37)
< 65 yrs	198/8315	71/4676		1.62 (1.13 to 2.32)
Sex			0.63	
Female	217/6663	111/5446		1.61 (1.19 to 2.19)
Male	22/5350	19/5830		1.31 (0.60 to 2.86)
Race/ethnicity			0.03	
Hispanics	15/596	8/636		2.05 (0.82 to 5.13)
NHW	91/5415	56/5801		1.75 (1.14 to 2.69)
NHB	109/4724	31/2802		2.19 (1.42 to 3.36)
Others	16/1322	37/2006		0.64 (0.32 to 1.29)
Obesity			0.81	
Yes	205/9454	82/5813		1.58 (1.09 to 2.28)
No	34/2586	47/5362		1.47 (0.94 to 2.29)
Coronary artery disease			0.42	
Yes	16/1558	8/1965		2.29 (0.97 to 5.45)
No	214/10 476	122/9301		1.57 (1.16 to 2.13)
Chronic kideny disease			0.30	
Yes	15/1086	10/1784		2.42 (1.04 to 5.61)
No	213/10 931	125/9483		1.5 (1.11 to 2.04)
Hypertension			0.91	
Yes	142/7176	84/6626		1.59 (1.14 to 2.2)
No	83/4869	49/4650		1.65 (0.98 to 2.76)
Entry year			0.57	
2023-2024	177/7392	132/8850		1.6 (1.21 to 2.13)
2019-2022	38/4618	9/2468		2.2 (0.75 to 6.43)
Insulin use			0.79	
Yes	57/4003	37/4419		1.71 (1.06 to 2.75)
No	171/8061	94/6794		1.58 (1.12 to 2.22)
Metformin use			0.61	
Yes	153/7128	103/6984		1.46 (1.01 to 2.12)
No	71/4918	37/4256		1.72 (1.04 to 2.86)
Type of GLP-1RA			0.15	
Semaglutide	102/5032	122/11 210		1.86 (1.29 to 2.66)
Tirzepatide	5/279	102/11 275		5.55 (1.43 to 21.45)
Liraglutide	17/1492	114/11 234		1.17 (0.71 to 1.92)
Dulaglutide	83/4668	119/11 290		1.67 (1.23 to 2.26)



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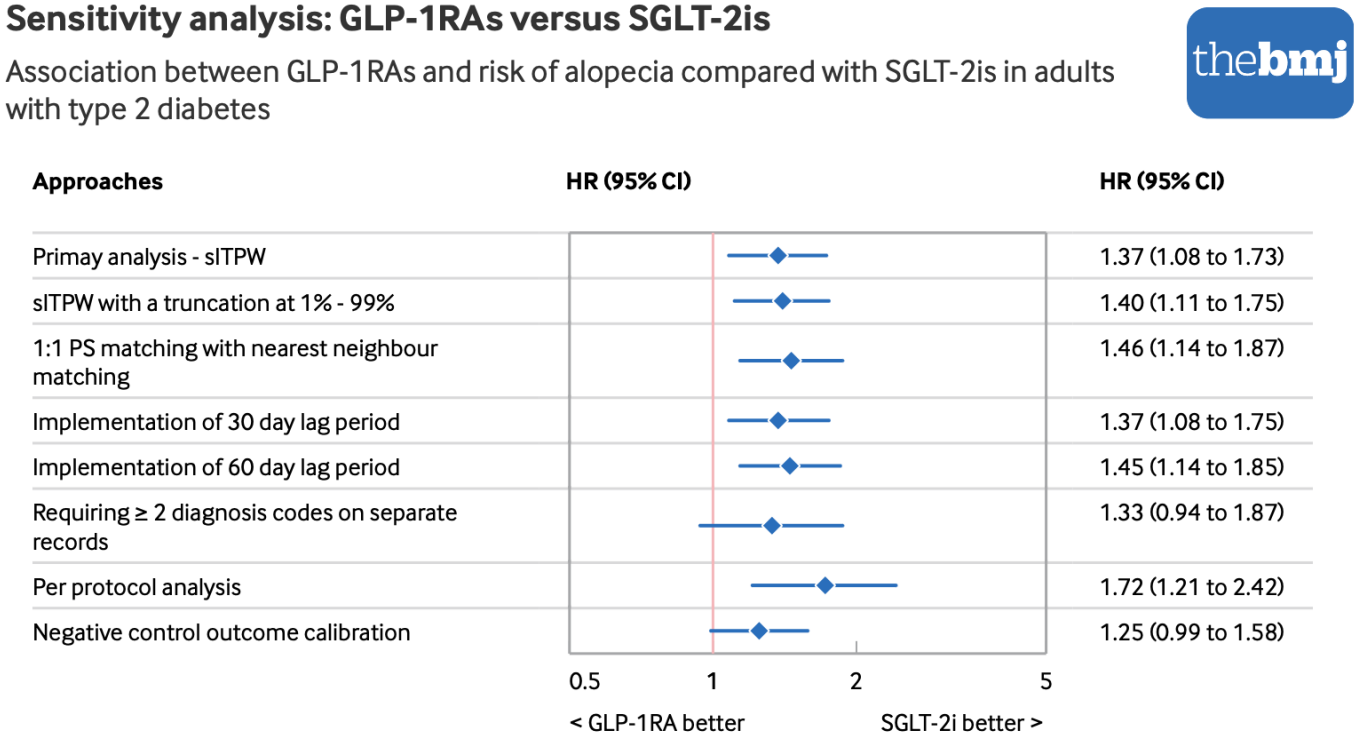
DPP-4i=dipeptidyl peptidase-4 inhibitor; GLP-1RA=glucagon-like peptide-1 receptor agonist; NHB=non-Hispanic black; NHW=non-Hispanic white

Fig 3 | Subgroup analysis of association between glucagon-like peptide-1 receptor agonists and risk of alopecia compared with dipeptidyl peptidase-4 inhibitors. An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/29535637/



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CI=confidence interval; GLP-1RA=glucagon-like peptide-1 receptor agonist; HR=hazard ratio; PS=propensity score; SGLT-2i=sodium-glucose cotransporter 2 inhibitor; sIPTW=stabilised inverse probability of treatment weighting

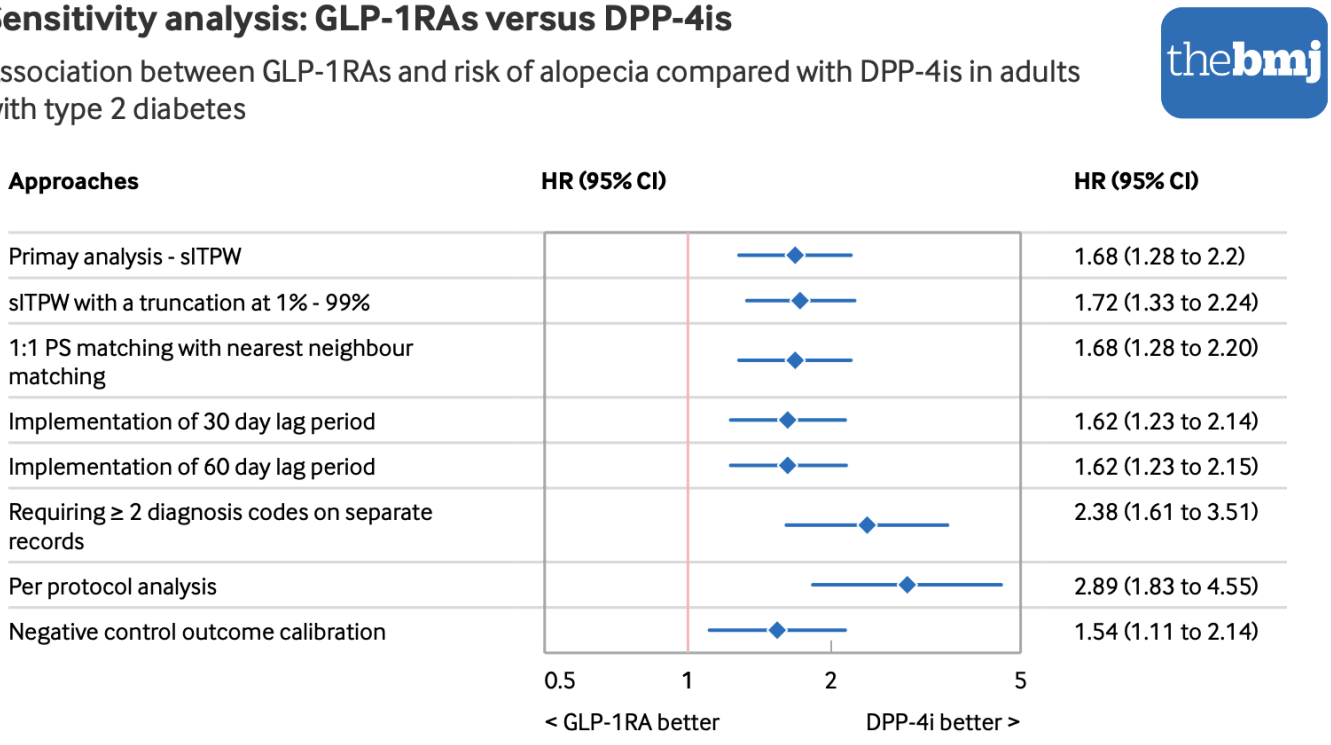
Fig 4 | Sensitivity analysis of association between glucagon-like peptide-1 receptor agonists and risk of alopecia compared with sodium-glucose cotransporter-2 inhibitors. An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/29559964/

of alopecia with semaglutide and tirzepatide, whereas no clear signal was observed for other GLP-1 receptor agonists.[7] In addition, a small observational study of 283 patients seen in a dermatology clinic described a potential increase in alopecia among GLP-1 receptor agonist users, although findings were descriptive and not formally adjusted for confounding.[5] A case report of semaglutide associated alopecia areata further described hair re-growth following drug discontinuation and dermatological treatment, suggesting reversibility in at least some cases.[30]

These previous reports provide early signals, but they were limited by small sample sizes, lack of comparator groups, and limited control for confounding,[5 7] Our results add to this literature in several important ways. Firstly, by using active comparators (SGLT-2 inhibitors and DPP-4 inhibitors), our study reduces confounding by indication and provides a more clinically relevant comparison between commonly used glucose lowering therapies. Secondly, the application of a target trial emulation framework, combined with robust adjustment for confounders, strengthens the internal validity of the findings relative to previous observational reports. Thirdly, the large sample size and longitudinal follow-up enable more precise estimation of risk and assessment of temporal patterns, including the concentration of events in the first year after treatment initiation.

In addition, our subtype specific analyses provide further clinical context by suggesting that the observed association is primarily driven by non-scarring forms of alopecia (for example, telogen effluvium), which are often reversible and may be related to systemic or metabolic stressors.[31] This aligns with previous clinical observations linking rapid weight loss, nutritional changes, and metabolic shifts to telogen effluvium.[31] However, evidence directly evaluating GLP-1 receptor agonist use in relation to specific alopecia subtypes remains limited, and further research is needed to better characterise these patterns.

Subgroup analyses were generally consistent across clinically relevant strata, supporting the



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DPP-4i=dipeptidyl peptidase 4 inhibitor; CI=confidence interval; GLP-1RA=glucagon-like peptide-1 receptor agonist; HR=hazard ratio; PS=propensity score; sIPTW=stabilised inverse probability of treatment weighting

Fig 5 | Sensitivity analysis of association between glucagon-like peptide-1 receptor agonists and risk of alopecia compared with dipeptidyl peptidase-4 inhibitors. An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/29560631/

overall findings. However, these results should be interpreted cautiously, as subgroup analyses may be underpowered and are susceptible to residual confounding and chance findings. Some heterogeneity was apparent for metformin use and race/ethnicity, but these findings are exploratory and may reflect underlying differences in patients' characteristics or healthcare use. Further studies are needed to confirm potential effect modification.

Biological mechanisms

The most likely mechanism underlying the observed association between GLP-1 receptor agonist use and alopecia relates to weight loss and reduced caloric

Table 3 | Risk of alopecia associated with GLP-1RAs compared with SGLT2is and DPP4is, in adults with type 2 diabetes

	GLP-1RA *v* SGLT-2i		GLP-1RA *v* DPP-4i	
	GLP-1RA	SGLT-2i	GLP-1RA	DPP-4i
Before sIPTW				
No of events/patients at risk	276/12 004	131/15 221	274/11 964	103/11 233
Mean (SD) follow-up, years	2.66 (1.70)	2.03 (1.59)	2.65 (1.70)	3.10 (1.68)
IR per 1000 person years	8.65	4.25	8.64	2.96
Hazard ratio (95% CI)	2.06 (1.67 to 2.54)	Reference	2.91 (2.32 to 3.65)	Reference
After sIPTW				
No of events/patients at risk	198/11 991	182/15 323	229/12 030	128/11 195
Mean (SD) follow-up, years	2.39 (1.66)	2.36 (1.68)	2.91 (1.69)	2.95 (1.70)
IR per 1000 person years	6.91	5.04	6.53	3.89
Hazard ratio (95% CI)	1.37 (1.08 to 1.73)	Reference	1.68 (1.28 to 2.20)	Reference

CI=confidence interval; DPP-4i=dipeptidyl peptidase-4 inhibitor; GLP-1RA=glucagon-like peptide-1 receptor agonist; IR=incidence rate; SD=standard deviation; SGLT-2i=sodium-glucose cotransporter-2 inhibitor; sIPTW=stabilised inverse probability of treatment weight.

Table 4 | Risk of subtype specific alopecia associated with GLP-1RAs compared with SGLT2is and DPP4is, in adults with type 2 diabetes

	GLP-1 RA *v* SGLT 2i		GLP-1 RA *v* DPP-4i	
Outcomes	GLP-1 RA	SGLT-2i	GLP-1 RA	DPP-4i
Alopecia areata				
No of events/patients at risk	12/11 991	14/15 323	14/12 030	7/11 195
Mena (SD) follow-up, years	2.42 (1.69)	2.38 (1.69)	2.94 (1.69)	2.96 (1.70)
IR per 1000 person years	0.40	0.37	0.40	0.22
Hazard ratio (95% CI)	1.09 (0.47 to 2.50)	Reference	1.78 (0.61 to 5.25)	Reference
Androgenic alopecia				
No of events/patients at risk	24/11 991	24/15 323	25/12 030	14/11 195
Mena (SD) follow-up, years	2.41 (1.67)	2.38 (1.69)	2.94 (1.69)	2.96 (1.70)
IR per 1000 person years	0.84	0.66	0.71	0.42
Hazard ratio (95% CI)	1.27 (0.68 to 2.36)	Reference	1.69 (0.82 to 3.48)	Reference
Other non-scarring alopecia*				
No of events/patients at risk	170/11 991	141/15 323	200/12 030	110/11 195
Mena (SD) follow-up, years	2.39 (1.66)	2.36 (1.69)	2.91 (1.69)	2.95 (1.70)
IR per 1000 person years	5.94	3.90	5.71	3.32
Hazard ratio (95% CI)	1.53 (1.18 to 1.97)	Reference	1.72 (1.28 to 2.31)	Reference
Cicatricial alopecia				
No of events/patients at risk	24/11 991	28/15 323	28/12 030	7/11 195
Mena (SD) follow-up, years	2.41 (1.67)	2.38 (1.69)	2.94 (1.69)	2.96 (1.70)
IR per 1000 person years	0.84	0.76	1.21	0.80
Hazard ratio (95% CI)	1.10 (0.56 to 2.16)	Reference	3.83 (1.55 to 9.46)	Reference

CI, confidence interval; DPP-4i=dipeptidyl peptidase-4 inhibitor; GLP-1RA=glucagon-like peptide-1 receptor agonist; IR=incidence rate; SD=standard deviation; SGLT-2i=sodium-glucose cotransporter-2 inhibitor.
*Includes telogen effluvium, angagen effluvium, alopecia mucinosa, and other non-scaring hair loss.

intake following treatment initiation. Rapid or substantial weight loss is a well established trigger of telogen effluvium, a form of diffuse, non-scarring hair shedding.[32 33] Caloric restriction may also contribute to physiological stress and micronutrient deficiencies (for example, iron, zinc, biotin), which can disrupt the hair growth cycle.[34] This aligns with the predominance of non-scarring alopecia observed in our study and suggests that hair loss may reflect downstream effects of metabolic change rather than a direct drug effect. Other contributing factors may include the broad metabolic, hormonal, and immunological effects attributed to GLP-1 receptor agonists that may influence hair follicle growth and cycling.[35] Firstly, a leading explanation. For example, hormonal alterations may be relevant.[36] GLP-1 receptor agonists have been associated with changes in thyroid function,[37] and delayed gastric emptying may alter the absorption of orally administered drugs,[38] including thyroid hormone or sex hormone therapies. Such changes could influence hair growth through endocrine mechanisms, particularly in individuals with underlying hormonal conditions. GLP-1 signalling has immunomodulatory properties.[39 40] Associations between GLP-1 receptor agonist use and certain immune mediated conditions, such as psoriasis, have been reported,[41] and these conditions are linked to autoimmune hair disorders such as alopecia areata.[42 43] However, we did not observe a clear association with alopecia areata, which does not support a predominant autoimmune mechanism in this setting. Further studies are needed to clarify underlying mechanisms, especially to assess the extent to which weight loss mediates the observed association.

Strengths and limitations of study

Our study has several strengths, including a representative national population using largely unselected Penn Medicine data, the use of a target trial emulation framework, rigorous adjustment for baseline confounding using sIPTW, and consistent findings from multiple sensitivity and subgroup analyses. By further distinguishing between alopecia subtypes, this study provides additional clinical specificity to a previously under-characterised potential safety signal.

Nevertheless, several limitations should be considered. Firstly, as with all observational studies, residual confounding cannot be fully excluded. Although we applied multiple strategies to mitigate confounding, including an active comparator, new user design, sIPTW, and negative control outcome calibration, these approaches may not fully account for unmeasured factors such as disease severity, lifestyle characteristics, or family history of alopecia that are not routinely captured in electronic health record data. In addition, E value analyses suggest that an unmeasured confounder of at least moderate strength would be needed to fully explain away the observed association. Secondly, we identified alopecia by using diagnostic codes recorded in routinely collected clinical data, which may be subject to misclassification and under-ascertainment, particularly for androgenetic alopecia and telogen effluvium, as well as milder or transient cases that do not prompt medical evaluation. Although we used a validated coding algorithm with a high positive predictive value,[19] the lack of detailed clinical information limited our ability to assess important dimensions of disease burden, including the severity, extent, duration, reversibility after treatment

discontinuation, and standardised clinical grading (for example, Hamilton-Norwood scale) of alopecia, as well as dermatologist confirmed assessments such as trichoscopy or scalp biopsy. As a result, our findings primarily reflect clinically documented, healthcare seeking cases of alopecia rather than the full spectrum of disease in the underlying population, which may be higher. To improve outcome specificity and reduce potential misclassification, we did a sensitivity analysis requiring at least two diagnosis codes recorded on separate encounters, which yielded consistent results.

Thirdly, we defined the exposure on the basis of prescribing data recorded in the electronic health record, which may result in exposure misclassification, as prescriptions do not guarantee dispensing of the medication or actual adherence by the patient. Patients may not start treatment (primary non-adherence), may discontinue early, or may deviate from prescribed regimens, and such information is not fully captured in routine electronic health record data. In addition, treatment switching or augmentation during follow-up may further contribute to exposure misclassification in an intention-to-treat framework. Although we mitigated these problems through sensitivity analyses, including a per protocol approach that censored follow-up at treatment discontinuation or switching, residual exposure misclassification cannot be completely excluded. Fourthly, diagnosis of alopecia depends on healthcare encounters, and differences in healthcare use between exposure groups could lead to differential outcome detection. Although we implemented several mitigation strategies, including adjustment for baseline healthcare use, negative control outcome calibration, and confirmation of balanced healthcare use during follow-up (supplementary table S6), the possibility of residual differential detection bias cannot be fully excluded.

Clinical implications

Although the absolute risk of clinically recorded alopecia associated with GLP-1 receptor agonist use is low, the observed association may still influence patients' satisfaction, adherence, and decisions to start or continue therapy. Hair loss is a patient valued outcome, and even cases captured in routine clinical care may be important for shared decision making. Importantly, non-scarring alopecia, the most commonly observed subtype, has often been linked to rapid weight loss and is typically reversible,[31] which may help to reassure patients and support continued therapy when clinically indicated.

Clinicians may consider discussing the possibility of hair loss when initiating GLP-1 receptor agonist therapy and monitoring for symptoms during follow-up, particularly in the first year. Supportive measures such as ensuring adequate nutrition, reviewing concurrent factors that may contribute to hair loss, and referral to dermatology when appropriate may be needed. These findings also highlight the need for ongoing surveillance of dermatological adverse events in GLP-1 receptor agonist users. Future studies incorporating patient reported outcomes and more detailed clinical assessments may help to better characterise the frequency, severity, and reversibility of alopecia and to inform strategies to minimise its impact while preserving the metabolic benefits of treatment of GLP-1 receptor agonists.

Conclusions

In conclusion, use of GLP-1 receptor agonists was associated with a higher incidence of clinically recorded hair loss, particularly non-scarring alopecia, in patients with type 2 diabetes, compared with SGLT-2 inhibitors and DPP-4 inhibitors. Although the absolute risk was small, awareness of this potential effect may support informed, patient centred treatment decisions. Further studies are needed to clarify underlying mechanisms, assess clinical severity and reversibility, and identify patients who may be at higher risk.

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Data sharing: The data used in this study are derived from Penn Medicine electronic health records and are not publicly available owing to patient privacy protections and institutional policies. Sample analytical code used for statistical analyses is publicly available and can be found at: https://github.com/Penncil/GLP1RA_hairloss/tree/master.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: We plan to disseminate our findings through various channels to the public, patients, and clinicians, including traditional media, social media, podcasts for healthcare professionals, and clinical and academic conferences.

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