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New-Onset Alopecia Is Significantly Higher with Tirzepatide than with Semaglutide, Even After Weight-Loss Matching

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Abstract

Alopecia is an emerging concern during tirzepatide or semaglutide therapy for weight management, but whether it is a consequence of weight loss or reflects incretin-specific biology remains unclear. Here we conduct an observational study comparing new users of tirzepatide (Zepbound, Mounjaro) or semaglutide (Wegovy, Ozempic, Rybelsus) with at least two prescriptions, no documented alopecia prior to the first prescription, and complete 12-month follow-up. Incident alopecia was defined using harmonized diagnosis codes and AI-curated clinical notes. Propensity-score matching was performed to balance tirzepatide and semaglutide users on age, race, sex, baseline BMI, and type 2 diabetes. In the matched cohorts (n=12,863 per arm), incident alopecia was more frequent with tirzepatide than with semaglutide (4.20% vs 2.88%; risk ratio [RR]: 1.46; 95% CI [1.28-1.66]; P<0.001). After additional matching on achieved weight loss (n=11,046 per arm), incident alopecia remained significantly higher after tirzepatide than semaglutide (4.24% versus 3.33%; RR: 1.27 [1.11-1.45]; P<0.001). By 6 months, incident alopecia had occurred in 1.55% of tirzepatide users versus 1.24% of semaglutide users, widening by 12 months to 4.20% versus 2.88%, respectively (hazard ratio [HR]: 1.46 [1.28-1.67]; log-rank P<0.001). Incident alopecia remained significantly more frequent with tirzepatide than semaglutide across clinically relevant strata (all P<0.001), including among patients with 20-to-30% weight loss, a range highlighted in pivotal obesity trials (RR: 1.44); in the low and high maximum-dose strata (RR: 1.76 and 1.39, respectively); and among patients with 4-6 prescriptions, a proxy for longer treatment duration (RR: 1.65). Analysis of newly initiated hair-loss therapies showed significantly higher minoxidil (Rogaine) initiation after tirzepatide than after semaglutide (RR, 2.04; P=0.002). Among 8,985 female patients, incident alopecia occurred in 5.44% of tirzepatide users versus 3.63% of semaglutide users (RR: 1.50 [1.31-1.72]; P<0.001), with significant differences in the 10-to-20% weight-loss band (RR: 1.41 [1.11-1.78]; P=0.004) and in the 20-to-30% weight-loss band (RR, 1.47; 95% CI, 1.06 to 2.04; P=0.018). Among tirzepatide users, incident-alopecia developers were more often female than non-developers (90.6% vs 68.9%, SMD: +0.56), and were enriched for underlying endocrine conditions including menstrual irregularity (20.0% vs 13.9%, SMD: +0.17), hypothyroidism (28.1% vs 21.6%, SMD: +0.15), and polycystic ovarian syndrome (6.7% vs 3.6%, SMD: +0.14). Repeated measurements of ferritin, iron, vitamin B12, folate, vitamin D, and zinc showed no significant nutrient decline accompanying incident alopecia. Exploratory single-cell RNA-seq analyses showed no *GLP1R* or *GIPR* expression in scalp follicular keratinocytes and identified multiple dermato-immune cell types that expressed *GIPR* but not *GLP1R*. Overall, in routine care, incident alopecia was higher after initiation of tirzepatide than semaglutide, motivating prospective comparative studies of incretin-based therapies.

Keywords: Alopecia; GLP1RA

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Introduction

Tirzepatide and semaglutide have transformed the pharmacologic treatment of obesity and type 2 diabetes by producing weight reduction of a magnitude previously seen mainly after bariatric procedures. In SURMOUNT-1, tirzepatide produced mean body-weight reductions of 15.0%, 19.5%, and 20.9% at 5 mg, 10 mg, and 15 mg, respectively, at 72 weeks [1]. In STEP 1, semaglutide 2.4 mg produced a mean body-weight reduction of 14.9% at 68 weeks [2]. In direct comparisons, tirzepatide has produced greater reductions in body weight than semaglutide, both in type 2 diabetes and, more recently, in obesity without type 2 diabetes [3,4].

As incretin-based pharmacotherapy has moved into broad clinical use, adverse-event interpretation has become complex. Some events may reflect direct pharmacologic effects, whereas others may reflect the physiologic consequences of rapid or substantial weight loss. Hair loss is a salient example. Telogen effluvium is a temporary diffuse hair loss disorder that may follow metabolic stress, hormonal change, illness, medication exposure, caloric restriction, or rapid weight loss [5,6]. Nutritional factors, including iron, proteinemia, and certain vitamins , are measured as part of the clinical evaluation of this condition [7].

The current prescribing information for both Zepbound and Wegovy describe hair-loss as an adverse reaction associated with weight reduction. In the Zepbound label, hair loss was reported in 5%, 4%, and 5% of patients receiving tirzepatide 5 mg, 10 mg, and 15 mg, respectively, versus 1% with placebo; in pooled weight-reduction trials, hair loss was reported more frequently among female than male patients, 7.1% versus 0.5% with Zepbound and 1.3% versus 0% with placebo [8]. In the Wegovy label, hair loss was reported in 3.3% of adults treated with semaglutide 2.4 mg versus 1.0% of placebo recipients, with higher reporting among women than men; higher-dose semaglutide trials also showed greater hair-loss reporting [8,9]. These observations support a weight-loss-associated mechanism, but they do not resolve whether the risk differs between tirzepatide and semaglutide at comparable weight loss, dose exposure, or treatment persistence.

This distinction is clinically important. If alopecia is largely a nonspecific consequence of weight loss, counseling can emphasize anticipatory guidance, nutritional surveillance, evaluation for potentially reversible contributors, and the tempo of weight reduction. If a residual between-drug difference persists after accounting for achieved weight loss, additional mechanisms may need to be considered, including fine-grained differences in GLP-1R versus GIPR pharmacology, receptor bias, dosing dynamics, nutritional effects, or other therapeutic distinctions. We therefore performed a real-world analysis to compare the incidence of alopecia and hair loss directed therapy initiation among propensity-matched cohorts of patients initiating tirzepatide versus semaglutide. Methodologically, this study evaluates a multi-signal pharmacovigilance framework combining structured diagnosis codes, AI-curated clinical notes, assertion status, event timing, medication new starts, active-comparator matching, weight-loss-band matching, and negative-control phenotypes.

Methods

Study Design, Data Source, and Cohort Definition

We conducted a retrospective, active-comparator, new-user (incident-user) pharmacoepidemiologic study using de-identified electronic health record (EHR) data accessed through the nference federated network, spanning more than 30 million patients, and reported it in accordance with the STROBE and RECORD frameworks [10,11]. Tirzepatide initiators (index arm) were compared head-to-head with semaglutide initiators as an active comparator within the same therapeutic class, following new-user design principles [12,13]. The index date was the first-ever recorded prescription of the index drug on or after January 1, 2022. To enforce incident, mutually exclusive cohorts, a washout window from 365 days before to 12 months after index required no prescription of any other glucagon-like peptide-1 (GLP-1) receptor agonist during the window (for the tirzepatide arm, semaglutide, dulaglutide, exenatide, or liraglutide; for the semaglutide arm, tirzepatide, dulaglutide, exenatide, or liraglutide); only GLP-1

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receptor agonists were washout-excluding, and patients whose first qualifying prescription was of both study drugs were excluded from both arms. To ensure complete follow-up, patients were required to have at least one recorded clinical event on or after 12 months following index, establishing evidence of continued EHR activity at or beyond 12 months, and all primary analyses were restricted to repeat-prescription patients with at least two prescriptions of the index drug (the index fill plus at least one additional distinct fill) within that window.

Baseline was defined as the period on or before index. Baseline body weight, body-mass index (BMI), and glycated hemoglobin (HbA1c) were each taken as the most recent qualifying measurement within 365 days before index; baseline comorbidities, alopecia-associated conditions, and type 2 diabetes status were defined as any corresponding International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis at any time on or before index, or a matching AI-curated clinical-note mention before index. Observed follow-up was defined as the interval from index to the last recorded clinical event, and prior use of hair-loss-directed medications (minoxidil, finasteride, dutasteride, spironolactone, bimatoprost, and Janus kinase inhibitors) was defined as any such prescription before index.

Cohort Construction and Analytic Populations

Eligibility criteria, sequential cohort attrition, exclusion of prevalent alopecia, and derivation of the unmatched and propensity-score–matched analytic populations are summarized in **Figure 1**. The primary five-covariate matched cohort included 12,863 tirzepatide users and 12,863 semaglutide users, and the secondary cohort additionally balanced on achieved weight-loss band included 11,046 patients per treatment arm. **Figure 1** also summarizes the combined ICD-10-CM and AI-curated clinical-note framework used to ascertain incident alopecia.

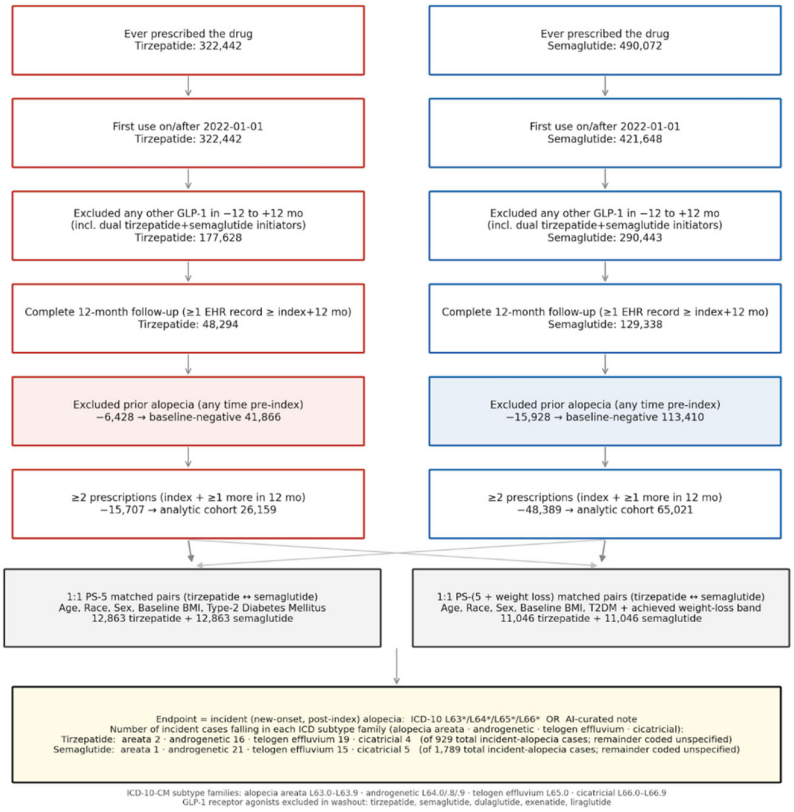

Figure 1. Cohort construction for the head-to-head analysis of new-onset alopecia after tirzepatide versus semaglutide initiation. Shown is the cohort attrition and matched-cohort construction for new users of

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tirzepatide and semaglutide in the federated electronic health record network. Eligible patients had evidence of ever being prescribed tirzepatide or semaglutide, first use on or after January 1, 2022, exclusion of any other GLP-1 receptor agonist exposure from 12 months before through 12 months after index, and complete 12-month follow-up. Patients with any pre-index alopecia diagnosis were then excluded, yielding a baseline-negative population of 41,866 tirzepatide users and 113,410 semaglutide users; requiring at least two prescriptions—the index prescription plus at least one additional prescription within 12 months—then yielded the analytic cohort of 26,159 tirzepatide users and 65,021 semaglutide users. Two 1:1 propensity-score matched cohorts were then generated from the analytic cohort: a five-covariate matched cohort balanced on age, race, sex, baseline body-mass index, and type 2 diabetes mellitus, with 12,863 patients in each arm, and a second matched cohort additionally balanced on achieved weight-loss band, with 11,046 patients in each arm. The endpoint was incident, new-onset post-index alopecia, identified through ICD-10-CM alopecia codes or AI-curated clinical notes. ICD-10-CM subtype families included alopecia areata, androgenetic alopecia, telogen effluvium, and cicatricial alopecia; most incident events were captured through AI-curated clinical notes without subtype-specific ICD coding. GLP-1 denotes glucagon-like peptide-1; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; PS, propensity score; T2DM, type 2 diabetes mellitus.

Propensity Matching and Weight-Loss Stratification

Patients with any alopecia at baseline (a structured ICD-10-CM diagnosis of L63, L64, L65, or L66 at any time on or before index, or an AI-curated clinical-note mention before index) were removed to form the baseline-negative analytic cohort, so that every remaining patient was at risk for incident alopecia; this exclusion was applied before matching and both unmatched and matched analyses were conducted within the same alopecia-free, at-risk population. Propensity scores were estimated by logistic regression of tirzepatide (versus semaglutide) assignment on five baseline covariates (age at index, sex, race, baseline BMI, and baseline type 2 diabetes status), with categorical covariates one-hot encoded and the first level dropped [14]. Tirzepatide and semaglutide patients were matched 1:1 by greedy nearest-neighbor matching on the logit of the propensity score within a caliper of 0.2 standard deviations of the logit, restricted to patients with complete covariate data [15]; this defined the primary propensity-score matched cohort of 12,863 patients per treatment arm, with post-matching balance summarized in **Table 1**. A second matched cohort was constructed from a propensity-score model that additionally included the achieved weight-loss band, balancing the arms on achieved weight loss and yielding 11,046 patients per treatment arm, with balance summarized in **Table 2**. Matching was performed separately in the overall population and within prespecified sex subgroups (the female subgroup being of primary interest), each restricted to the repeat-prescription cohort, and balance was assessed by the standardized mean difference (SMD), with an absolute SMD of at least 0.1 taken to indicate meaningful residual imbalance [16].

Achieved weight loss was defined as (baseline weight − nadir weight)/baseline weight × 100, where baseline weight was the closest measurement within 365 days before index and nadir weight was the minimum recorded weight during the 12-month post-index observation window. Patients were stratified by achieved weight loss into five disjoint bands (≤5%, 5–10%, 10–20%, 20–30%, and 30–40%).

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Table 1. Baseline Characteristics before and after Five-Covariate Propensity-Score Matching. Shown are baseline demographic, cardiometabolic, endocrine, nutritional, dermatologic, alopecia-related, reproductive, stress-related, and prior hair-loss-treatment characteristics among semaglutide and tirzepatide users before matching (in the unmatched baseline-negative cohort with at least two prescriptions) and after 1:1 propensity-score matching on age, race, sex, baseline body-mass index, and type 2 diabetes. Values are mean (SD) for continuous variables and percentage (number) for categorical variables. For each period, standardized mean differences (SMDs) are shown for between-group balance; rows marked with an asterisk and bolded indicate residual imbalance with absolute SMD greater than 0.10 after matching. Before matching, the analytic cohort included 65,021 semaglutide users and 26,159 tirzepatide users; the matched cohort included 12,863 semaglutide users and 12,863 tirzepatide users.

Characteristic	Before matching (unmatched)			After matching (PS-5)		
	Semaglutide	Tirzepatide	SMD	Semaglutide	Tirzepatide	SMD
N patients	65,021	26,159		12,863	12,863	
Age at index, years	54.3 (14.0)	52.1 (12.9)	-0.165	50.7 (13.8)	50.7 (13.0)	+0.000
Follow-up, months *	**24.2 (8.3)**	**21.0 (7.4)**	**-0.406**	**23.1 (7.9)**	**20.7 (7.5)**	**-0.318**
BMI, kg/m²	36.2 (5.6)	36.2 (6.1)	-0.000	36.3 (5.9)	36.2 (6.1)	-0.021
HbA1c, %	7.1 (1.8)	6.7 (1.7)	-0.178	6.1 (1.3)	6.0 (1.2)	-0.081
Weight, kg	106.1 (23.7)	106.9 (24.4)	+0.034	105.7 (23.2)	106.3 (23.8)	+0.025
Female sex	61.8% (40192)	64.5% (16865)	+0.055	70.2% (9034)	69.8% (8982)	-0.009
White / Caucasian	73.8% (48015)	81.0% (21191)	+0.172	83.5% (10741)	83.2% (10700)	-0.009
Black / African American	18.2% (11849)	11.4% (2971)	-0.194	10.8% (1383)	10.8% (1393)	+0.003
Asian	1.7% (1106)	1.5% (385)	-0.018	1.1% (137)	1.1% (147)	+0.007
Hypertension	74.0% (48085)	69.2% (18113)	-0.105	67.9% (8739)	67.0% (8612)	-0.021
Hyperlipidemia	62.4% (40556)	58.7% (15343)	-0.076	57.2% (7360)	56.9% (7323)	-0.006
ASCVD	6.5% (4231)	6.7% (1747)	+0.007	13.7% (1765)	11.6% (1488)	-0.065
Heart failure	1.9% (1206)	1.6% (430)	-0.016	4.5% (581)	3.1% (404)	-0.072
Atrial fibrillation	1.9% (1210)	2.2% (585)	+0.027	4.7% (599)	4.2% (545)	-0.020
Obesity	79.3% (51576)	80.9% (21174)	+0.041	87.2% (11215)	86.3% (11105)	-0.025
Type 2 diabetes	8.8% (5744)	11.1% (2915)	+0.077	19.9% (2566)	20.6% (2654)	+0.017
Diabetes complications	5.0% (3267)	5.9% (1556)	+0.041	11.5% (1482)	11.1% (1434)	-0.012
Hypothyroidism	19.8% (12878)	20.6% (5376)	+0.019	22.5% (2899)	21.9% (2818)	-0.015
Hashimoto thyroiditis	0.7% (461)	1.3% (333)	+0.057	2.0% (263)	2.4% (315)	+0.027
Other thyroiditis	3.0% (1963)	3.3% (869)	+0.017	3.5% (456)	3.9% (508)	+0.021
Hyperthyroidism / thyrotoxicosis	5.3% (3438)	5.2% (1364)	-0.003	5.9% (754)	5.5% (707)	-0.016
Thyroid nodules or nontoxic goiter	8.3% (5375)	8.1% (2126)	-0.005	9.1% (1165)	9.7% (1245)	+0.021
Iron-deficiency anemia	3.5% (2280)	4.7% (1223)	+0.059	9.3% (1193)	8.9% (1148)	-0.012
Vitamin B12 deficiency anemia	0.4% (287)	0.6% (154)	+0.021	1.2% (160)	1.2% (148)	-0.009
Folate deficiency anemia	0.0% (25)	0.1% (22)	+0.018	0.1% (15)	0.2% (22)	+0.014
Other nutritional anemia	0.3% (192)	0.3% (86)	+0.006	0.8% (104)	0.6% (82)	-0.020

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Unspecified anemia	4.6% (2988)	5.3% (1381)	+0.032	11.8% (1513)	10.0% (1289)	-0.056
Vitamin D deficiency	9.0% (5866)	12.9% (3371)	+0.124	24.3% (3131)	24.7% (3171)	+0.007
Vitamin B12 deficiency	0.0% (2)	0.0% (0)	-0.008	0.0% (2)	0.0% (0)	-0.018
Folate deficiency	0.1% (55)	0.1% (35)	+0.015	0.2% (29)	0.2% (31)	+0.003
Zinc or trace-element deficiency	1.2% (805)	1.7% (434)	+0.035	3.1% (404)	3.2% (407)	+0.001
Protein-calorie malnutrition	3.4% (2203)	2.7% (713)	-0.038	3.1% (396)	2.7% (348)	-0.022
Abnormal weight loss	0.0% (0)	0.0% (0)		0.0% (0)	0.0% (0)	
Loss of appetite / anorexia	4.9% (3178)	4.7% (1223)	-0.010	5.5% (713)	4.6% (596)	-0.041
Eating disorder	0.8% (543)	1.2% (310)	+0.035	1.8% (229)	1.9% (243)	+0.008
Bariatric surgery history	0.0% (1)	0.0% (0)	-0.006	0.0% (0)	0.0% (0)	
Intestinal malabsorption	2.5% (1640)	2.9% (746)	+0.020	3.7% (473)	4.0% (518)	+0.018
Systemic lupus erythematosus	0.2% (139)	0.3% (68)	+0.009	0.7% (84)	0.5% (64)	-0.021
Rheumatoid arthritis	1.0% (664)	1.2% (323)	+0.020	3.1% (396)	2.3% (294)	-0.049
Psoriasis	5.6% (3668)	5.8% (1507)	+0.005	6.4% (817)	6.1% (790)	-0.009
Vitiligo	0.4% (264)	0.4% (94)	-0.008	0.4% (57)	0.4% (50)	-0.008
Atopic dermatitis / eczema	9.7% (6305)	9.2% (2412)	-0.016	9.8% (1263)	10.0% (1289)	+0.007
Seborrheic dermatitis	0.8% (552)	1.2% (312)	+0.034	2.4% (309)	2.3% (298)	-0.006
Contact dermatitis	2.0% (1300)	3.2% (836)	+0.075	6.4% (818)	6.1% (784)	-0.011
Tinea capitis / dermatophytosis	4.8% (3108)	5.6% (1472)	+0.038	8.1% (1047)	8.1% (1041)	-0.002
Scalp infection / folliculitis	6.5% (4211)	7.0% (1830)	+0.021	9.4% (1215)	9.5% (1221)	+0.002
Polycystic ovary syndrome	1.2% (759)	2.0% (515)	+0.065	3.5% (453)	3.7% (474)	+0.009
Ovarian dysfunction / hyperandrogenic endocrine disorder	1.7% (1107)	2.7% (701)	+0.067	4.4% (563)	4.8% (613)	+0.019
Hirsutism / androgen-excess phenotype	2.3% (1479)	2.5% (647)	+0.013	2.4% (315)	2.4% (310)	-0.003
Menstrual irregularity / amenorrhea	7.7% (5035)	9.6% (2508)	+0.066	13.7% (1764)	14.1% (1815)	+0.011
Menopause / ovarian failure	7.5% (4898)	8.6% (2255)	+0.040	10.9% (1399)	11.9% (1534)	+0.033
Pregnancy or postpartum state	7.1% (4631)	8.8% (2314)	+0.064	12.8% (1641)	12.4% (1592)	-0.011
Major surgery or postoperative state	24.5% (15950)	26.4% (6917)	+0.044	27.6% (3546)	27.4% (3524)	-0.004
Acute severe infection or hospitalization	5.0% (3249)	4.0% (1036)	-0.050	4.7% (607)	3.4% (439)	-0.066
COVID-19 history	37.7% (24518)	38.5% (10079)	+0.017	40.5% (5211)	41.1% (5287)	+0.012
Cancer history	44.0% (28631)	41.9% (10958)	-0.043	43.8% (5640)	44.6% (5737)	+0.015
Chemotherapy exposure	0.1% (63)	0.1% (27)	+0.002	0.1% (10)	0.1% (16)	+0.015

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Chronic kidney disease	4.0% (2599)	3.9% (1010)	-0.007	9.7% (1245)	7.5% (961)	-0.079
Chronic liver disease	6.0% (3920)	7.2% (1875)	+0.046	11.1% (1427)	11.1% (1424)	-0.001
Depression	65.6% (42623)	66.2% (17311)	+0.013	70.8% (9112)	68.3% (8788)	-0.055
Anxiety disorder	13.9% (9023)	20.2% (5275)	+0.168	41.0% (5269)	38.2% (4919)	-0.056
Stress or adjustment disorder	1.9% (1235)	2.5% (653)	+0.041	5.6% (725)	4.8% (613)	-0.039
Dermatology visit history	0.0% (0)	0.0% (0)		0.0% (0)	0.0% (0)	
Prior minoxidil prescription	0.2% (125)	0.2% (63)	+0.010	0.2% (21)	0.2% (26)	+0.009
Prior finasteride prescription	1.7% (1129)	1.5% (381)	-0.022	1.2% (160)	1.2% (156)	-0.003
Prior dutasteride prescription	0.2% (148)	0.2% (48)	-0.010	0.2% (23)	0.1% (19)	-0.008
Prior spironolactone prescription	8.2% (5309)	7.3% (1904)	-0.033	6.6% (845)	6.5% (833)	-0.004
Prior bimatoprost prescription	0.6% (373)	0.7% (174)	+0.012	0.5% (63)	0.7% (93)	+0.030
Prior baricitinib prescription	0.1% (51)	0.1% (23)	+0.003	0.0% (5)	0.0% (6)	+0.004
Prior ritlecitinib prescription	0.0% (0)	0.0% (0)		0.0% (0)	0.0% (0)	
Prior deuruxolitinib prescription	0.0% (0)	0.0% (0)		0.0% (0)	0.0% (0)	
Prior tofacitinib prescription	0.2% (114)	0.2% (50)	+0.004	0.1% (18)	0.2% (27)	+0.017
Prior upadacitinib prescription	0.1% (47)	0.1% (26)	+0.009	0.1% (19)	0.1% (13)	-0.013

Table 2. Baseline Characteristics after Propensity-Score Matching with Additional Balance on Achieved Weight-Loss Band Shown are baseline demographic, cardiometabolic, endocrine, nutritional, dermatologic, alopecia-related, reproductive, stress-related, and prior hair-loss-treatment characteristics among semaglutide and tirzepatide users after 1:1 propensity-score matching on age, race, sex, baseline body-mass index, type 2 diabetes, and achieved weight-loss band. Values are mean (SD) for continuous variables and percentage (number) for categorical variables. Standardized mean differences (SMDs) are shown for between-group balance; rows marked with an asterisk and bolded indicate residual imbalance with absolute SMD greater than 0.10 after matching. The matched cohort included 11,046 semaglutide users and 11,046 tirzepatide users.

Characteristic	**Semaglutide**	**Tirzepatide**	**SMD**
N patients	11,046	11,046	
Age at index, years	51.1 (14.1)	51.0 (13.3)	-0.007
Follow-up, months *	**23.1 (7.9)**	**20.5 (7.4)**	**-0.343**
BMI, kg/m²	36.2 (5.7)	36.3 (6.1)	+0.005
HbA1c, %	6.1 (1.3)	6.0 (1.3)	-0.066
Weight, kg	105.4 (22.7)	106.4 (23.9)	+0.043
Female sex	70.1% (7739)	69.7% (7697)	-0.008
White / Caucasian	82.0% (9060)	82.1% (9067)	+0.002
Black / African American	12.2% (1348)	11.9% (1310)	-0.011
Asian	1.0% (108)	1.2% (132)	+0.021
Hypertension	69.5% (7675)	68.1% (7517)	-0.031
Hyperlipidemia	58.8% (6491)	57.8% (6380)	-0.020
ASCVD	14.8% (1640)	12.2% (1344)	-0.078
Heart failure	4.9% (544)	3.3% (367)	-0.081

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Atrial fibrillation	4.7% (524)	4.4% (491)	-0.014
Obesity	87.7% (9683)	86.4% (9541)	-0.038
Type 2 diabetes	21.8% (2406)	22.1% (2444)	+0.008
Diabetes complications	12.8% (1416)	12.1% (1335)	-0.022
Hypothyroidism	22.4% (2476)	22.0% (2427)	-0.011
Hashimoto thyroiditis	2.0% (221)	2.4% (262)	+0.025
Other thyroiditis	3.5% (385)	3.9% (429)	+0.021
Hyperthyroidism / thyrotoxicosis	5.9% (653)	5.6% (621)	-0.012
Thyroid nodules or nontoxic goiter	9.8% (1084)	10.0% (1102)	+0.005
Iron-deficiency anemia	9.6% (1057)	9.1% (1000)	-0.018
Vitamin B12 deficiency anemia	1.3% (146)	1.2% (128)	-0.015
Folate deficiency anemia	0.1% (14)	0.2% (18)	+0.010
Other nutritional anemia	0.9% (96)	0.6% (70)	-0.027
Unspecified anemia	12.2% (1349)	10.5% (1156)	-0.055
Vitamin D deficiency	24.5% (2710)	25.3% (2792)	+0.017
Vitamin B12 deficiency	0.0% (1)	0.0% (0)	-0.013
Folate deficiency	0.2% (20)	0.3% (28)	+0.016
Zinc or trace-element deficiency	3.6% (394)	3.3% (362)	-0.016
Protein-calorie malnutrition	3.7% (409)	2.9% (324)	-0.043
Abnormal weight loss	0.0% (0)	0.0% (0)	
Loss of appetite / anorexia	5.7% (632)	4.4% (487)	-0.060
Eating disorder	1.9% (210)	1.9% (209)	-0.001
Bariatric surgery history	0.0% (0)	0.0% (0)	
Intestinal malabsorption	4.0% (442)	4.1% (454)	+0.006
Systemic lupus erythematosus	0.6% (68)	0.5% (58)	-0.012
Rheumatoid arthritis	3.2% (357)	2.3% (255)	-0.056
Psoriasis	6.1% (679)	6.1% (676)	-0.001
Vitiligo	0.4% (48)	0.4% (44)	-0.006
Atopic dermatitis / eczema	10.5% (1163)	10.1% (1113)	-0.015
Seborrheic dermatitis	2.4% (261)	2.4% (270)	+0.005
Contact dermatitis	6.5% (714)	6.0% (660)	-0.020
Tinea capitis / dermatophytosis	8.5% (935)	8.3% (920)	-0.005
Scalp infection / folliculitis	9.6% (1064)	9.6% (1058)	-0.002
Polycystic ovary syndrome	3.4% (375)	3.6% (403)	+0.014
Ovarian dysfunction / hyperandrogenic endocrine disorder	4.3% (472)	4.7% (524)	+0.023
Hirsutism / androgen-excess phenotype	2.4% (261)	2.5% (272)	+0.006
Menstrual irregularity / amenorrhea	13.9% (1530)	13.9% (1538)	+0.002
Menopause / ovarian failure	11.6% (1279)	12.4% (1367)	+0.025
Pregnancy or postpartum state	12.6% (1388)	11.7% (1292)	-0.027
Major surgery or postoperative state	28.1% (3102)	27.1% (2991)	-0.022
Acute severe infection or hospitalization	4.9% (538)	3.6% (394)	-0.065
COVID-19 history	41.7% (4605)	41.6% (4590)	-0.003
Cancer history	46.1% (5088)	45.8% (5056)	-0.006
Chemotherapy exposure	0.1% (12)	0.1% (16)	+0.010
Chronic kidney disease	10.6% (1172)	8.0% (879)	-0.091
Chronic liver disease	11.4% (1264)	11.4% (1256)	-0.002
Depression	72.1% (7965)	68.2% (7532)	-0.086
Anxiety disorder	41.1% (4543)	38.1% (4206)	-0.062
Stress or adjustment disorder	5.6% (622)	4.8% (532)	-0.037
Dermatology visit history	0.0% (0)	0.0% (0)	
Prior minoxidil prescription	0.2% (25)	0.2% (24)	-0.002
Prior finasteride prescription	1.4% (156)	1.3% (144)	-0.009
Prior dutasteride prescription	0.2% (21)	0.2% (17)	-0.009
Prior spironolactone prescription	6.8% (749)	6.5% (721)	-0.010
Prior bimatoprost prescription	0.5% (55)	0.8% (84)	+0.033
Prior baricitinib prescription	0.0% (2)	0.0% (3)	+0.006
Prior ritlecitinib prescription	0.0% (0)	0.0% (0)	

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Prior deuruxolitinib prescription	0.0% (0)	0.0% (0)	
Prior tofacitinib prescription	0.2% (21)	0.2% (23)	+0.004
Prior upadacitinib prescription	0.2% (17)	0.1% (11)	-0.015

Endpoint Ascertainment, Incident-Alopecia, and Exposure-Intensity Analyses

The primary endpoint was incident alopecia, ascertained from both structured diagnosis codes and AI-curated clinical notes using a validated natural language processing (NLP) extraction pipeline [17–20]. A patient was counted as having incident alopecia if, within the incident window from 7 to 365 days after index (the 7-day lower bound imposing a minimum latency that excludes disease documented around initiation), they had either a structured ICD-10-CM diagnosis of L63, L64, L65, or L66 or an AI-curated clinical-note mention of alopecia (terms including alopecia, hair loss, hair thinning, effluvium, and hair shedding); the two ascertainment sources were harmonized into a single patient-level concept, and AI-curated mentions were restricted to high-confidence assertions of present disease (extraction probability of at least 0.8). A stratified sample of extracted phenotypes was previously adjudicated by physician reviewers, with extraction accuracy and inter-reviewer agreement reported in that prior validation work [17–20]. The combined code-and-note approach was used to reduce underascertainment from structured ICD coding alone, because many clinically documented hair-loss events lacked subtype-specific ICD codes. For a focused note-level analysis within the five-covariate matched cohort, hair-loss mentions were further classified hierarchically as affirmed, possible, or negated, with affirmed mentions taking precedence over possible or negated mentions for the same patient.

Because every analytic patient was baseline-negative by construction, all were at risk, and the incidence proportion was the number of incident cases divided by at-risk patients per arm; incident alopecia was compared between arms in the unmatched analytic cohort, the primary five-covariate matched cohort, and the weight-loss-band matched cohort, and incident cases were additionally partitioned into those captured through AI-curated notes versus structured ICD-coded subtypes, with counts tabulated for four subtype families (alopecia areata, L63; androgenetic alopecia, L64; telogen effluvium, L65.0; and cicatricial or scarring alopecia, L66). Ascertainment-source and ICD-coded subtype distributions are presented for the unmatched and five-covariate matched cohorts in **Tables 3-4**, respectively, and overall incident-alopecia estimates across the three matching approaches are presented in **Table 5**. Within the five-covariate matched cohort, cumulative incidence of alopecia was calculated as the cumulative proportion of at-risk patients with a first incident event by each month of follow-up through month 12.

Table 3. Ascertainment and ICD-Coded Subtypes of Incident Alopecia in the Unmatched Cohort with Two or More Prescriptions Shown are incident alopecia events after tirzepatide or semaglutide initiation in the unmatched analytic cohort with at least two prescriptions. Alopecia ascertainment combined AI-curated clinical-note documentation with ICD-10-CM alopecia codes. Incidence percentages were calculated as incident cases divided by the treatment-specific analytic cohort size: 26,159 tirzepatide users and 65,021 semaglutide users. Risk ratios compare tirzepatide with semaglutide incidence. Counts fewer than 11 are masked as <11. ICD-10-CM subtype families included alopecia areata, androgenetic alopecia, telogen effluvium, and cicatricial or scarring alopecia. *This is a restricted, subtype-attributable ascertainment: the overall (any-subtype) total counts only the four named ICD families shown — alopecia areata (L63), androgenetic alopecia (L64), telogen effluvium (L650), and cicatricial/scarring alopecia (L66) — plus AI-note cases. It is therefore lower than the primary incident-alopecia count (Table 5), which additionally captures unspecified or other nonscarring alopecia (ICD L651-L659) not attributable to a named family.*

subtype	sublabel	icd	sema_ icd	sema_ note	sema_ total	Sema_ incidence_%	tirz _icd	tirz_ note	tirz_ total	Tirz_ incidence_%	RR_tirz_ vs_sema
Alopecia areata	Alopecia totalis	L630	<11	<11	<11	0.0	<11	<11	<11	0.0	

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Alopecia areata	Alopecia universalis	L631	<11	<11	<11	0.0	<11	<11	<11	0.0	
Alopecia areata	Ophiasis	L632	<11	<11	<11	0.0	<11	<11	<11	0.0	
Alopecia areata	Other alopecia areata	L638	<11	<11	<11	0.0	<11	<11	<11	0.0	
Alopecia areata	Alopecia areata, unspecified	L639	<11	<11	<11	0.0015	<11	<11	<11	0.0076	4.971
Alopecia areata	Subtotal, alopecia areata	L63	<11	<11	<11	0.0015	<11	<11	<11	0.0076	4.971
Androgenetic alopecia	Drug-induced androgenic alopecia	L640	<11	<11	<11	0.0015	<11	<11	<11	0.0076	4.971
Androgenetic alopecia	Other androgenic alopecia	L648	<11	<11	<11	0.0062	<11	<11	<11	0.0	
Androgenetic alopecia	Androgenic alopecia, unspecified	L649	16	<11	16	0.0246	14	<11	14	0.0535	2.175
Androgenetic alopecia	Subtotal, androgenetic alopecia	L64	21	<11	21	0.0323	16	<11	16	0.0612	1.894
Telogen effluvium	Telogen effluvium	L650	15	<11	15	0.0231	19	<11	19	0.0726	3.148
Cicatricial / scarring alopecia	Pseudopelade	L660	<11	<11	<11	0.0	<11	<11	<11	0.0	
Cicatricial / scarring alopecia	Lichen planopilaris	L661	<11	<11	<11	0.0	<11	<11	<11	0.0038	
Cicatricial / scarring alopecia	Folliculitis decalvans	L662	<11	<11	<11	0.0015	<11	<11	<11	0.0	
Cicatricial / scarring alopecia	Perifolliculitis capitis abscedens	L663	<11	<11	<11	0.0015	<11	<11	<11	0.0	
Cicatricial / scarring alopecia	Folliculitis ulerythematosa reticulata	L664	<11	<11	<11	0.0	<11	<11	<11	0.0	
Cicatricial / scarring alopecia	Other cicatricial alopecia	L668	<11	<11	<11	0.0031	<11	<11	<11	0.0038	1.243
Cicatricial / scarring alopecia	Cicatricial alopecia, unspecified	L669	<11	<11	<11	0.0046	<11	<11	<11	0.0076	1.657
Cicatricial / scarring alopecia	Subtotal, cicatricial / scarring alopecia	L66	<11	<11	<11	0.0077	<11	<11	<11	0.0153	1.988
Any of four alopecia subtypes	Overall total	L63, L64, L650 ,L66	39	1777	1789	2.7514	37	926	929	3.5514	1.291

Table 4. Ascertainment and ICD-Coded Subtypes of Incident Alopecia in the Five-Covariate Propensity-Score Matched Cohort. Shown are incident alopecia events after tirzepatide or semaglutide initiation in the five-covariate propensity-score matched cohort. Alopecia ascertainment combined AI-curated clinical-note documentation with ICD-10-CM alopecia codes. Incidence percentages were calculated as incident cases divided by the treatment-specific matched cohort size: 12,863 tirzepatide users and 12,863 semaglutide users. Risk ratios compare tirzepatide with semaglutide incidence. Counts fewer than 11 are masked as <11. ICD-10-CM subtype

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families included alopecia areata, androgenetic alopecia, telogen effluvium, and cicatricial or scarring alopecia. PS-5 denotes propensity-score matching on age, race, sex, baseline body-mass index, and type 2 diabetes. *This is a restricted, subtype-attributable ascertainment: the overall (any-subtype) total counts only the four named ICD families shown — alopecia areata (L63), androgenetic alopecia (L64), telogen effluvium (L650), and cicatricial/scarring alopecia (L66) — plus AI-note cases, and is therefore lower than the primary matched incident-alopecia count in Table 5 (540 vs 371), which additionally captures unspecified or other nonscarring alopecia (ICD L651-L659).*

subtype	sublabel	icd	sema_icd	sema_note	sema_total	sema_incidence_%	tirz_icd	tirz_note	tirz_total	tirz_incidence_%	RR_tirz_vs_sema
Alopecia areata	Alopecia totalis	L630	<11	<11	<11	0.0	<11	<11	<11	0.0	
Alopecia areata	Alopecia universalis	L631	<11	<11	<11	0.0	<11	<11	<11	0.0	
Alopecia areata	Ophiasis	L632	<11	<11	<11	0.0	<11	<11	<11	0.0	
Alopecia areata	Other alopecia areata	L638	<11	<11	<11	0.0	<11	<11	<11	0.0	
Alopecia areata	Alopecia areata, unspecified	L639	<11	<11	<11	0.0	<11	<11	<11	0.0155	
Alopecia areata	Subtotal, alopecia areata	L63	<11	<11	<11	0.0	<11	<11	<11	0.0155	
Androgenetic alopecia	Drug-induced androgenic alopecia	L640	<11	<11	<11	0.0	<11	<11	<11	0.0155	
Androgenetic alopecia	Other androgenic alopecia	L648	<11	<11	<11	0.0078	<11	<11	<11	0.0	
Androgenetic alopecia	Androgenic alopecia, unspecified	L649	<11	<11	<11	0.0777	12	<11	12	0.0933	1.2
Androgenetic alopecia	Subtotal, androgenetic alopecia	L64	11	<11	11	0.0855	14	<11	14	0.1088	1.273
Telogen effluvium	Telogen effluvium	L650	<11	<11	<11	0.0622	18	<11	18	0.1399	2.25
Cicatricial / scarring alopecia	Pseudopelade	L660	<11	<11	<11	0.0	<11	<11	<11	0.0	
Cicatricial / scarring alopecia	Lichen planopilaris	L661	<11	<11	<11	0.0	<11	<11	<11	0.0078	
Cicatricial / scarring alopecia	Folliculitis decalvans	L662	<11	<11	<11	0.0	<11	<11	<11	0.0	
Cicatricial / scarring alopecia	Perifolliculitis capitis abscedens	L663	<11	<11	<11	0.0	<11	<11	<11	0.0	
Cicatricial / scarring alopecia	Folliculitis ulerythematosa reticulata	L664	<11	<11	<11	0.0	<11	<11	<11	0.0	

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Cicatricial / scarring alopecia	Other cicatricial alopecia	L668	<11	<11	<11	0.0	<11	<11	<11	0.0078	
Cicatricial / scarring alopecia	Cicatricial alopecia, unspecified	L669	<11	<11	<11	0.0	<11	<11	<11	0.0155	
Cicatricial / scarring alopecia	Subtotal, cicatricial / scarring alopecia	L66	<11	<11	<11	0.0	<11	<11	<11	0.0311	
Any of four alopecia subtypes	Overall total	L63,L64,L650,L666	17	350	354	2.7521	34	499	502	3.9027	1.418

Table 5. Overall Incident Alopecia after Tirzepatide versus Semaglutide Initiation across Matching Approaches. Shown are 12-month incident new-onset alopecia rates after tirzepatide or semaglutide initiation in the unmatched cohort, the five-covariate propensity-score matched cohort (PS-5 matched), and the propensity-score matched cohort additionally balanced on achieved weight-loss band (PS-5 + weight-loss band). Values are percentage (number of incident alopecia cases/number of patients at risk). Risk ratios compare tirzepatide with semaglutide. P values are from two-proportion tests. PS-5 denotes propensity-score matching on age, race, sex, baseline body-mass index, and type 2 diabetes.

Cohort	Tirzepatide	Semaglutide	RR (95% CI)	p
Unmatched	3.73% (975/26159)	2.80% (1819/65021)	1.33 (1.23-1.44)	<0.001
PS-5 matched	4.20% (540/12863)	2.88% (371/12863)	1.46 (1.28-1.66)	<0.001
PS-5 + weight-loss band	4.24% (468/11046)	3.33% (368/11046)	1.27 (1.11-1.45)	<0.001

Table 6. Propensity-matched analysis of new Starts of Hair-Loss-Directed Therapies after Tirzepatide versus Semaglutide Initiation. Shown are post-index new starts of hair-loss-directed therapies among baseline-negative 1:1 five-covariate propensity-score (PS-5) matched cohort (12,863 patients per arm). Values are the number of new starters and percentage of the treatment-specific analytic cohort. Risk ratios compare new-starter incidence after tirzepatide with that after semaglutide. Confidence intervals are shown for each risk ratio, and P values compare between-group incidence. Counts fewer than 11 are masked as <11. Total denotes the combined number of new starters across both treatment groups.

drug	display	tirz_new	tirz_pct	sema_new	sema_pct	RR	ci	p	total
minoxidil	Minoxidil	53	0.412	26	0.202	2.038	1.28-3.26	0.0023469020994207	79
finasteride_1mg	Finasteride (1mg)	<11	0.023	<11	0.023	1.0	0.20-4.95	1.0	6
bimatoprost	Bimatoprost/Latisse	27	0.21	17	0.132	1.588	0.87-2.91	0.1313377357935553	44
tofacitinib	Tofacitinib/Xeljanz	<11	0.047	<11	0.047	1.0	0.32-3.10	1.0	12
upadacitinib	Upadacitinib/Rinvoq	<11	0.054	13	0.101	0.538	0.21-1.35	0.1795432793191879	20
baricitinib	Baricitinib	<11	0.0	<11	0.0				0
ritlecitinib	Ritlecitinib	<11	0.0	<11	0.0				0
deuruxolitinib	Deuruxolitinib	<11	0.0	<11	0.0				0
propecia	Propecia	<11	0.023	<11	0.023	1.0	0.20-4.95	1.0	6

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Dose-Tier Stratification for Comparing Semaglutide and Tirzepatide

For the analysis shown in **Figure 2D**, maximum achieved dose during the 12-month post-index period was dichotomized within each drug's approved dose range. For tirzepatide, lower maximum dose was defined as less than 10 mg (2.5, 5, or 7.5 mg) and higher maximum dose as 10 mg or greater (10, 12.5, or 15 mg). For subcutaneous semaglutide, lower maximum dose was defined as less than 1.0 mg (0.25 or 0.5 mg) and higher maximum dose as 1.0 mg or greater (1.0, 2.0, or 2.4 mg). Low-versus-low and high-versus-high comparisons therefore contrasted the lower and upper dose tiers within each drug's respective dosing scale rather than equal absolute milligram doses.

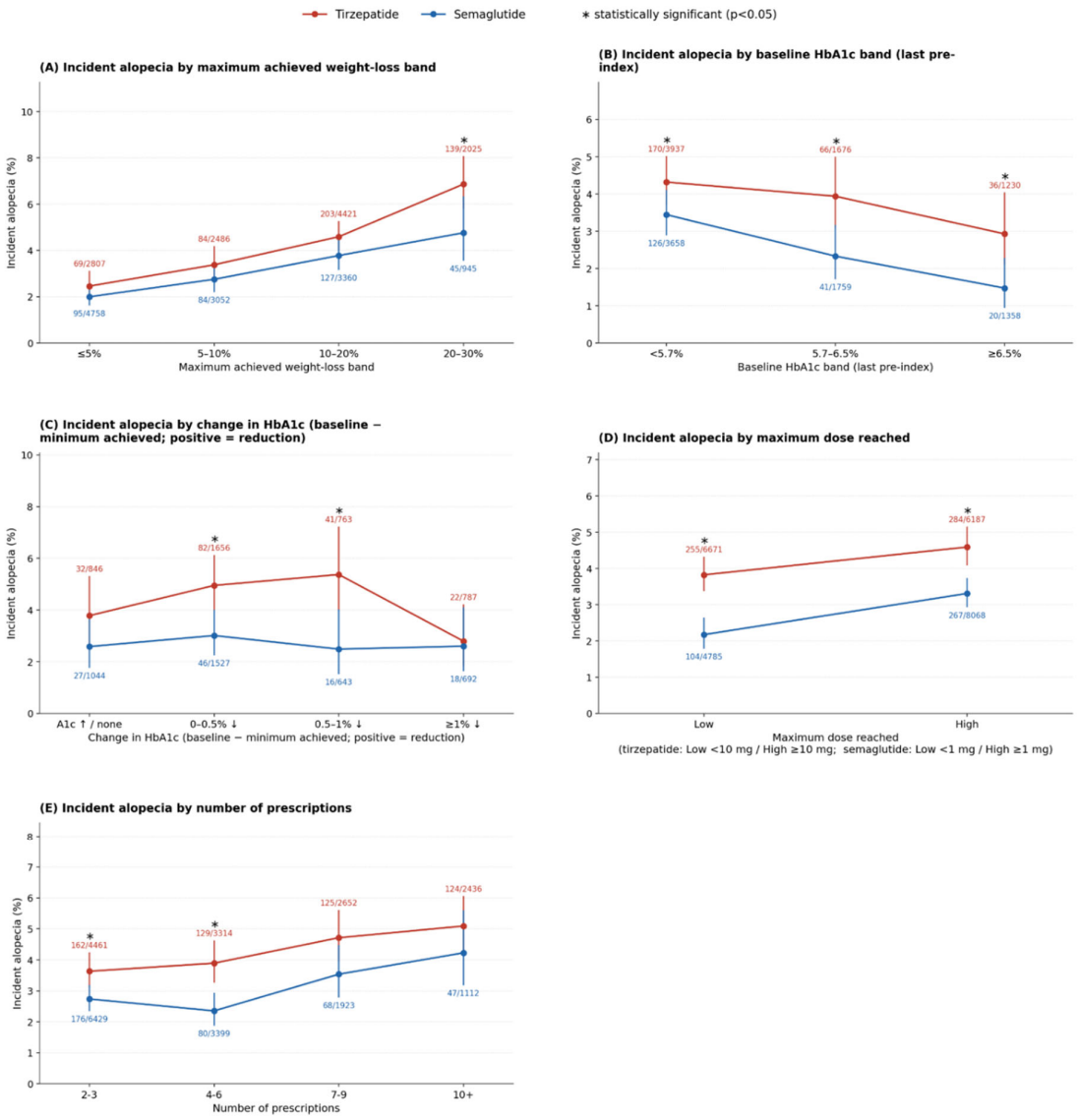

Figure 2. Incident Alopecia According to Weight-Loss, Glycemic, Dose, and Prescription-Exposure Strata. Shown are 12-month rates of incident new-onset alopecia among propensity-score matched tirzepatide and semaglutide users (n=12,863/arm) by: **(A)** maximum achieved weight-loss band; **(B)** baseline HbA1c band; **(C)** change in HbA1c (baseline − minimum achieved, capturing the maximum within-patient reduction; positive values indicate a reduction); **(D)** maximum dose reached; and **(E)** number of prescriptions. Points indicate observed incidence percentages, vertical bars indicate 95% confidence intervals, and labels show the number of incident alopecia cases over the number of patients at risk; counts fewer than 11 are shown as "<11." Asterisks indicate statistically significant between-group differences at P<0.05. Across all panels, the pooled risk ratio for tirzepatide versus semaglutide was 1.46 (95% CI, 1.28 to 1.66; P<0.001). HbA1c denotes glycated hemoglobin.

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Paired Vitamin and Mineral Laboratory Analysis

Among patients in the five-covariate propensity-score–matched cohort, paired vitamin and mineral laboratory trajectories were evaluated separately among patients who developed incident alopecia and those who did not. The analysis included ferritin, iron, vitamin B12, folate, 25-hydroxy vitamin D, and zinc and was restricted, for each laboratory test, to patients with both a pre-index and post-index measurement. Pre-index and post-index values were summarized as mean (SD), and within-patient change was summarized using Cohen's d, calculated as the mean paired post-minus-pre difference divided by the standard deviation of the paired differences. Results for incident-alopecia developers and non-developers are presented in **Tables 7A and 7B**, respectively.

Table 7. A. Paired Pre-Index and Post-Index Vitamin and Mineral Laboratory Values Among Patients Who Developed Incident Alopecia, in the Five-Covariate Propensity-Score Matched Cohort. Shown are paired laboratory values among patients in the five-covariate propensity-score matched cohort who developed incident (new-onset, post-index) alopecia and who had both a pre-index and post-index measurement for each vitamin or mineral test. Values are mean (SD). The paired sample size indicates the number of patients with both measurements available. Cohen's d was calculated as the mean paired post-minus-pre difference divided by the standard deviation of the paired difference. Labs shown include ferritin, iron, vitamin B12, folate, 25-hydroxy vitamin D, and zinc. This table is intended for direct comparison with Table 7B (patients who did not develop alopecia), to assess whether alopecia onset was accompanied by any lowering of these laboratory values. PS-5 denotes propensity-score matching on age, race, sex, baseline body-mass index, and type 2 diabetes. **B. Paired Pre-Index and Post-Index Vitamin and Mineral Laboratory Values Among Patients Who Did Not Develop Incident Alopecia, in the Five-Covariate Propensity-Score Matched Cohort.** Shown are paired laboratory values among patients in the five-covariate propensity-score matched cohort who did not develop incident alopecia (the remainder of the cohort after excluding the incident-alopecia developers in Table 7A) and who had both a pre-index and post-index measurement for each vitamin or mineral test. Values are mean (SD). The paired sample size indicates the number of patients with both measurements available. Cohen's d was calculated as the mean paired post-minus-pre difference divided by the standard deviation of the paired difference. Labs shown include ferritin, iron, vitamin B12, folate, 25-hydroxy vitamin D, and zinc. Comparison with Table 7A shows that within-patient laboratory trajectories among alopecia developers were similar to, or slightly greater than, those among non-developers, providing no evidence that incident alopecia was accompanied by a decline in these vitamin or mineral levels. PS-5 denotes propensity-score matching on age, race, sex, baseline body-mass index, and type 2 diabetes.

(A)								
Lab	**Tirzepatide pre, mean (SD)**	**Tirzepatide post, mean (SD)**	**Tirzepatide n paired**	**Tirzepatide Cohen's d (post-pre)**	**Semaglutide pre, mean (SD)**	**Semaglutide post, mean (SD)**	**Semaglutide n paired**	**Semaglutide Cohen's d (post-pre)**
Ferritin	100.3 (161.9)	147.0 (253.3)	42	+0.31	69.9 (174.9)	134.8 (316.4)	34	+0.21
Iron	76.0 (28.0)	73.2 (37.5)	25	-0.08	62.0 (29.8)	71.6 (31.5)	24	+0.26
Vitamin B12	506.1 (276.4)	509.8 (242.8)	43	+0.01	587.8 (390.4)	611.3 (361.2)	29	+0.06
Folate	12.7 (5.7)	13.8 (8.4)	12	+0.12	13.8 (4.4)	11.5 (5.6)	11	-0.60
25-Hydroxy vitamin D	35.9 (20.7)	44.5 (19.3)	70	+0.45	31.7 (14.4)	37.4 (18.8)	46	+0.33
Zinc			0		0.8 (0.1)	0.7 (0.1)	<11	-1.02
(B)								
Lab	**Tirzepatide pre, mean (SD)**	**Tirzepatide post, mean (SD)**	**Tirzepatide n paired**	**Tirzepatide Cohen's d (post-pre)**	**Semaglutide pre, mean (SD)**	**Semaglutide post, mean (SD)**	**Semaglutide n paired**	**Semaglutide Cohen's d (post-pre)**
Ferritin	98.7 (189.3)	126.7 (240.6)	536	+0.14	120.8 (208.3)	149.3 (260.7)	487	+0.17

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Iron	71.4 (38.6)	72.3 (35.7)	422	+0.02	72.0 (40.0)	73.2 (35.7)	403	+0.03
Vitamin B12	529.8 (381.4)	599.8 (367.2)	542	+0.17	515.0 (362.6)	567.3 (365.0)	473	+0.13
Folate	11.6 (5.2)	11.7 (5.5)	130	+0.01	11.4 (4.5)	11.9 (5.1)	122	+0.11
25-Hydroxy vitamin D	34.7 (17.8)	42.3 (20.3)	950	+0.42	35.5 (18.7)	40.7 (19.4)	900	+0.30
Zinc	24.8 (34.7)	24.3 (33.3)	53	-0.07	15.2 (27.9)	17.1 (29.4)	37	+0.22

Baseline Features Associated with Incident Alopecia

As a descriptive analysis, baseline demographic, anthropometric, cardiometabolic, endocrine, nutritional, dermatologic, reproductive, stress-related, and medication features were compared between patients who did and did not develop incident alopecia. Comparisons were conducted separately among tirzepatide users, semaglutide users, and the pooled five-covariate matched cohort (**Tables 8, 9, and 10**, respectively). SMDs were calculated as the value among incident-alopecia developers minus that among non-developers, and features were ranked according to the absolute SMD. These developer-versus-non-developer comparisons were considered descriptive rather than causal because they condition on a post-index event.

Table 8. Baseline Features Associated with Incident Alopecia among Tirzepatide Users in the Five-Covariate Propensity-Score Matched Cohort. Shown are baseline features among tirzepatide users who did versus did not develop incident new-onset alopecia in the five-covariate propensity-score matched cohort. Values are mean (SD) for continuous variables and percentage (number) for categorical variables. Standardized mean differences compare incident-alopecia developers with non-developers, calculated as developer minus non-developer; positive values indicate features that were higher or more prevalent among developers, and negative values indicate features that were lower or less prevalent among developers. Features are ranked by the absolute value of the standardized mean difference. The tirzepatide cohort included 540 incident-alopecia developers and 12,323 non-developers. PS-5 denotes propensity-score matching on age, race, sex, baseline body-mass index, and type 2 diabetes.

Baseline feature	Developers (N=540)	Non-developers (N=12,323)	SMD (dev vs non-dev)
Female sex	90.6% (489)	68.9% (8493)	+0.559
Weight, kg	100.8 (21.8)	106.5 (23.9)	-0.252
HbA1c, %	5.8 (0.9)	6.0 (1.2)	-0.184
Menstrual irregularity / amenorrhea	20.0% (108)	13.9% (1707)	+0.165
Ovarian dysfunction / hyperandrogenic endocrine disorder	8.5% (46)	4.6% (567)	+0.159
Hypothyroidism	28.1% (152)	21.6% (2666)	+0.151
Atrial fibrillation	1.9% (10)	4.3% (535)	-0.144
Other thyroiditis	7.0% (38)	3.8% (470)	+0.143
Hashimoto thyroiditis	5.0% (27)	2.3% (288)	+0.142
Polycystic ovary syndrome	6.7% (36)	3.6% (438)	+0.142
Black / African American	7.0% (38)	11.0% (1355)	-0.139
Thyroid nodules or nontoxic goiter	13.7% (74)	9.5% (1171)	+0.131
Seborrheic dermatitis	4.4% (24)	2.2% (274)	+0.124
Hypertension	61.5% (332)	67.2% (8280)	-0.119
Follow-up, months	19.8 (7.2)	20.7 (7.6)	-0.117
Chronic kidney disease	4.8% (26)	7.6% (935)	-0.115
Hyperlipidemia	51.5% (278)	57.2% (7045)	-0.114
Cancer history	50.0% (270)	44.4% (5467)	+0.113
Age at index, years	49.3 (12.8)	50.7 (13.0)	-0.112
Pregnancy or postpartum state	15.9% (86)	12.2% (1506)	+0.107
Menopause / ovarian failure	15.4% (83)	11.8% (1451)	+0.105

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Prior spironolactone prescription	9.1% (49)	6.4% (784)	+0.102
BMI, kg/m²	35.6 (6.2)	36.2 (6.0)	-0.097
Type 2 diabetes	17.0% (92)	20.8% (2562)	-0.096
White / Caucasian	86.3% (466)	83.0% (10234)	+0.090
Systemic lupus erythematosus	1.3% (7)	0.5% (57)	+0.089
Hirsutism / androgen-excess phenotype	3.9% (21)	2.3% (289)	+0.089
Unspecified anemia	7.8% (42)	10.1% (1247)	-0.082
ASCVD	9.3% (50)	11.7% (1438)	-0.079
Contact dermatitis	8.0% (43)	6.0% (741)	+0.077
Prior bimatoprost prescription	1.5% (8)	0.7% (85)	+0.076
Eating disorder	3.0% (16)	1.8% (227)	+0.073
Other nutritional anemia	0.2% (1)	0.7% (81)	-0.073
Vitamin D deficiency	27.6% (149)	24.5% (3022)	+0.070
Rheumatoid arthritis	3.3% (18)	2.2% (276)	+0.066
Depression	65.6% (354)	68.4% (8434)	-0.061
Loss of appetite / anorexia	5.9% (32)	4.6% (564)	+0.061
Folate deficiency anemia	0.0% (0)	0.2% (22)	-0.060
Protein-calorie malnutrition	1.9% (10)	2.7% (338)	-0.059
Heart failure	2.2% (12)	3.2% (392)	-0.059
Intestinal malabsorption	5.2% (28)	4.0% (490)	+0.058
Anxiety disorder	40.9% (221)	38.1% (4698)	+0.057
Prior dutasteride prescription	0.0% (0)	0.2% (19)	-0.056
Atopic dermatitis / eczema	11.7% (63)	9.9% (1226)	+0.055
Psoriasis	7.4% (40)	6.1% (750)	+0.053
Chemotherapy exposure	0.4% (2)	0.1% (14)	+0.052
Hyperthyroidism / thyrotoxicosis	6.7% (36)	5.4% (671)	+0.051
Scalp infection / folliculitis	10.9% (59)	9.4% (1162)	+0.050
Chronic liver disease	12.6% (68)	11.0% (1356)	+0.049
Tinea capitis / dermatophytosis	6.9% (37)	8.1% (1004)	-0.049
Asian	1.7% (9)	1.1% (138)	+0.047
Prior upadacitinib prescription	0.0% (0)	0.1% (13)	-0.046
Diabetes complications	9.8% (53)	11.2% (1381)	-0.045
Vitiligo	0.2% (1)	0.4% (49)	-0.039
Obesity	85.2% (460)	86.4% (10645)	-0.034
Prior minoxidil prescription	0.4% (2)	0.2% (24)	+0.033
Prior tofacitinib prescription	0.4% (2)	0.2% (25)	+0.031
Prior baricitinib prescription	0.0% (0)	0.0% (6)	-0.031
Major surgery or postoperative state	28.7% (155)	27.3% (3369)	+0.030
Prior finasteride prescription	0.9% (5)	1.2% (151)	-0.029
Iron-deficiency anemia	8.1% (44)	9.0% (1104)	-0.029
COVID-19 history	42.4% (229)	41.0% (5058)	+0.028
Folate deficiency	0.4% (2)	0.2% (29)	+0.025
Vitamin B12 deficiency anemia	0.9% (5)	1.2% (143)	-0.023
Zinc or trace-element deficiency	3.5% (19)	3.1% (388)	+0.021
Acute severe infection or hospitalization	3.7% (20)	3.4% (419)	+0.016
Stress or adjustment disorder	4.6% (25)	4.8% (588)	-0.007
Vitamin B12 deficiency	0.0% (0)	0.0% (0)	
Abnormal weight loss	0.0% (0)	0.0% (0)	
Bariatric surgery history	0.0% (0)	0.0% (0)	
Dermatology visit history	0.0% (0)	0.0% (0)	
Prior ritlecitinib prescription	0.0% (0)	0.0% (0)	
Prior deuruxolitinib prescription	0.0% (0)	0.0% (0)	

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Table 9. Baseline Features Associated with Incident Alopecia among Semaglutide Users in the Five-Covariate Propensity-Score Matched Cohort. Shown are baseline features among semaglutide users who did versus did not develop incident new-onset alopecia in the five-covariate propensity-score matched cohort. Values are mean (SD) for continuous variables and percentage (number) for categorical variables. Standardized mean differences compare incident-alopecia developers with non-developers, calculated as developer minus non-developer; positive values indicate features that were higher or more prevalent among developers, and negative values indicate features that were lower or less prevalent among developers. Features are ranked by the absolute value of the standardized mean difference. The semaglutide cohort included 371 incident-alopecia developers and 12,492 non-developers. PS-5 denotes propensity-score matching on age, race, sex, baseline body-mass index, and type 2 diabetes.

Baseline feature	Developers (N=371)	Non-developers (N=12,492)	SMD (dev vs non-dev)
Female sex	87.9% (326)	69.7% (8708)	+0.456
HbA1c, %	5.8 (1.2)	6.1 (1.4)	-0.250
Hypothyroidism	30.5% (113)	22.3% (2786)	+0.186
Hyperlipidemia	48.2% (179)	57.5% (7181)	-0.186
Other thyroiditis	7.3% (27)	3.4% (429)	+0.171
Age at index, years	48.5 (13.6)	50.7 (13.8)	-0.165
Weight, kg	102.1 (22.2)	105.8 (23.2)	-0.161
ASCVD	8.9% (33)	13.9% (1732)	-0.157
Rheumatoid arthritis	6.2% (23)	3.0% (373)	+0.154
Hypertension	61.2% (227)	68.1% (8512)	-0.146
Hashimoto thyroiditis	4.3% (16)	2.0% (247)	+0.134
Cancer history	50.1% (186)	43.7% (5454)	+0.130
COVID-19 history	46.4% (172)	40.3% (5039)	+0.122
Anxiety disorder	46.6% (173)	40.8% (5096)	+0.118
Other nutritional anemia	2.2% (8)	0.8% (96)	+0.116
Pregnancy or postpartum state	16.7% (62)	12.6% (1579)	+0.115
Tinea capitis / dermatophytosis	5.4% (20)	8.2% (1027)	-0.113
Hyperthyroidism / thyrotoxicosis	8.4% (31)	5.8% (723)	+0.100
Eating disorder	3.2% (12)	1.7% (217)	+0.096
Psoriasis	8.6% (32)	6.3% (785)	+0.089
Intestinal malabsorption	5.4% (20)	3.6% (453)	+0.085
Heart failure	3.0% (11)	4.6% (570)	-0.084
Polycystic ovary syndrome	5.1% (19)	3.5% (434)	+0.081
Protein-calorie malnutrition	4.6% (17)	3.0% (379)	+0.081
Hirsutism / androgen-excess phenotype	3.8% (14)	2.4% (301)	+0.079
Menstrual irregularity / amenorrhea	16.4% (61)	13.6% (1703)	+0.079
BMI, kg/m²	35.9 (6.0)	36.3 (5.9)	-0.074
Prior finasteride prescription	2.2% (8)	1.2% (152)	+0.073
Scalp infection / folliculitis	11.6% (43)	9.4% (1172)	+0.072
Folate deficiency	0.0% (0)	0.2% (29)	-0.068
Zinc or trace-element deficiency	4.3% (16)	3.1% (388)	+0.064
Prior dutasteride prescription	0.0% (0)	0.2% (23)	-0.061
Ovarian dysfunction / hyperandrogenic endocrine disorder	5.7% (21)	4.3% (542)	+0.061
Major surgery or postoperative state	30.2% (112)	27.5% (3434)	+0.060
Thyroid nodules or nontoxic goiter	10.8% (40)	9.0% (1125)	+0.060
Prior minoxidil prescription	0.0% (0)	0.2% (21)	-0.058
Type 2 diabetes	17.8% (66)	20.0% (2500)	-0.057
Vitamin D deficiency	26.7% (99)	24.3% (3032)	+0.055
Prior upadacitinib prescription	0.0% (0)	0.2% (19)	-0.055
Prior tofacitinib prescription	0.0% (0)	0.1% (18)	-0.054
Diabetes complications	10.0% (37)	11.6% (1445)	-0.051
Chronic liver disease	12.7% (47)	11.0% (1380)	+0.050

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Prior spironolactone prescription	7.8% (29)	6.5% (816)	+0.050
Atrial fibrillation	3.8% (14)	4.7% (585)	-0.045
Chemotherapy exposure	0.0% (0)	0.1% (10)	-0.040
Menopause / ovarian failure	9.7% (36)	10.9% (1363)	-0.040
Folate deficiency anemia	0.3% (1)	0.1% (14)	+0.036
Seborrheic dermatitis	3.0% (11)	2.4% (298)	+0.036
White / Caucasian	82.2% (305)	83.5% (10436)	-0.035
Vitamin B12 deficiency anemia	1.6% (6)	1.2% (154)	+0.032
Loss of appetite / anorexia	6.2% (23)	5.5% (690)	+0.029
Prior baricitinib prescription	0.0% (0)	0.0% (5)	-0.028
Asian	0.8% (3)	1.1% (134)	-0.027
Stress or adjustment disorder	6.2% (23)	5.6% (702)	+0.025
Depression	69.8% (259)	70.9% (8853)	-0.023
Systemic lupus erythematosus	0.8% (3)	0.6% (81)	+0.019
Chronic kidney disease	9.2% (34)	9.7% (1211)	-0.018
Vitamin B12 deficiency	0.0% (0)	0.0% (2)	-0.018
Iron-deficiency anemia	9.7% (36)	9.3% (1157)	+0.015
Unspecified anemia	11.3% (42)	11.8% (1471)	-0.014
Vitiligo	0.5% (2)	0.4% (55)	+0.014
Obesity	86.8% (322)	87.2% (10893)	-0.012
Follow-up, months	23.2 (8.1)	23.1 (7.9)	+0.012
Black / African American	11.1% (41)	10.7% (1342)	+0.010
Prior bimatoprost prescription	0.5% (2)	0.5% (61)	+0.007
Acute severe infection or hospitalization	4.6% (17)	4.7% (590)	-0.007
Contact dermatitis	6.5% (24)	6.4% (794)	+0.005
Atopic dermatitis / eczema	9.7% (36)	9.8% (1227)	-0.004
Abnormal weight loss	0.0% (0)	0.0% (0)	
Bariatric surgery history	0.0% (0)	0.0% (0)	
Dermatology visit history	0.0% (0)	0.0% (0)	
Prior ritlecitinib prescription	0.0% (0)	0.0% (0)	
Prior deuruxolitinib prescription	0.0% (0)	0.0% (0)	

Table 10. Baseline Features Associated with Incident Alopecia among Pooled Tirzepatide and Semaglutide Users in the Five-Covariate Propensity-Score Matched Cohort. Shown are baseline features among the pooled tirzepatide and semaglutide users who did versus did not develop incident new-onset alopecia in the five-covariate propensity-score matched cohort. Values are mean (SD) for continuous variables and percentage (number) for categorical variables. Standardized mean differences compare incident-alopecia developers with non-developers, calculated as developer minus non-developer; positive values indicate features that were higher or more prevalent among developers, and negative values indicate features that were lower or less prevalent among developers. Features are ranked by the absolute value of the standardized mean difference. The pooled cohort included 911 incident-alopecia developers and 24,815 non-developers. PS-5 denotes propensity-score matching on age, race, sex, baseline body-mass index, and type 2 diabetes.

Baseline feature	Developers (N=911)	Non-developers (N=24,815)	SMD (dev vs non-dev)
Female sex	89.5% (815)	69.3% (17201)	+0.514
HbA1c, %	5.8 (1.0)	6.0 (1.3)	-0.220
Weight, kg	101.3 (22.0)	106.2 (23.5)	-0.212
Hypothyroidism	29.1% (265)	22.0% (5452)	+0.164
Other thyroiditis	7.1% (65)	3.6% (899)	+0.156
Hyperlipidemia	50.2% (457)	57.3% (14226)	-0.144
Hashimoto thyroiditis	4.7% (43)	2.2% (535)	+0.141
Age at index, years	49.0 (13.1)	50.7 (13.4)	-0.134
Hypertension	61.4% (559)	67.7% (16792)	-0.132
Menstrual irregularity / amenorrhea	18.6% (169)	13.7% (3410)	+0.131

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Ovarian dysfunction / hyperandrogenic endocrine disorder	7.4% (67)	4.5% (1109)	+0.123
Cancer history	50.1% (456)	44.0% (10921)	+0.121
Polycystic ovary syndrome	6.0% (55)	3.5% (872)	+0.119
ASCVD	9.1% (83)	12.8% (3170)	-0.118
Pregnancy or postpartum state	16.2% (148)	12.4% (3085)	+0.109
Thyroid nodules or nontoxic goiter	12.5% (114)	9.3% (2296)	+0.105
Rheumatoid arthritis	4.5% (41)	2.6% (649)	+0.102
Atrial fibrillation	2.6% (24)	4.5% (1120)	-0.101
Follow-up, months	21.2 (7.8)	21.9 (7.8)	-0.090
BMI, kg/m²	35.7 (6.1)	36.3 (6.0)	-0.090
Seborrheic dermatitis	3.8% (35)	2.3% (572)	+0.089
Hirsutism / androgen-excess phenotype	3.8% (35)	2.4% (590)	+0.084
Eating disorder	3.1% (28)	1.8% (444)	+0.083
Prior spironolactone prescription	8.6% (78)	6.4% (1600)	+0.080
Type 2 diabetes	17.3% (158)	20.4% (5062)	-0.078
Chronic kidney disease	6.6% (60)	8.6% (2146)	-0.078
Heart failure	2.5% (23)	3.9% (962)	-0.077
Anxiety disorder	43.2% (394)	39.5% (9794)	+0.077
Tinea capitis / dermatophytosis	6.3% (57)	8.2% (2031)	-0.075
Black / African American	8.7% (79)	10.9% (2697)	-0.074
Intestinal malabsorption	5.3% (48)	3.8% (943)	+0.071
Hyperthyroidism / thyrotoxicosis	7.4% (67)	5.6% (1394)	+0.071
COVID-19 history	44.0% (401)	40.7% (10097)	+0.067
Psoriasis	7.9% (72)	6.2% (1535)	+0.067
Vitamin D deficiency	27.2% (248)	24.4% (6054)	+0.065
Systemic lupus erythematosus	1.1% (10)	0.6% (138)	+0.060
Scalp infection / folliculitis	11.2% (102)	9.4% (2334)	+0.059
Prior dutasteride prescription	0.0% (0)	0.2% (42)	-0.058
Unspecified anemia	9.2% (84)	11.0% (2718)	-0.058
Prior bimatoprost prescription	1.1% (10)	0.6% (146)	+0.056
Menopause / ovarian failure	13.1% (119)	11.3% (2814)	+0.053
Depression	67.3% (613)	69.7% (17287)	-0.051
Prior upadacitinib prescription	0.0% (0)	0.1% (32)	-0.051
Chronic liver disease	12.6% (115)	11.0% (2736)	+0.050
Diabetes complications	9.9% (90)	11.4% (2826)	-0.049
Contact dermatitis	7.4% (67)	6.2% (1535)	+0.047
Loss of appetite / anorexia	6.0% (55)	5.1% (1254)	+0.043
Major surgery or postoperative state	29.3% (267)	27.4% (6803)	+0.042
Zinc or trace-element deficiency	3.8% (35)	3.1% (776)	+0.039
White / Caucasian	84.6% (771)	83.3% (20670)	+0.036
Atopic dermatitis / eczema	10.9% (99)	9.9% (2453)	+0.032
Chemotherapy exposure	0.2% (2)	0.1% (24)	+0.031
Other nutritional anemia	1.0% (9)	0.7% (177)	+0.030
Prior baricitinib prescription	0.0% (0)	0.0% (11)	-0.030
Obesity	85.8% (782)	86.8% (21538)	-0.028
Asian	1.3% (12)	1.1% (272)	+0.020
Prior finasteride prescription	1.4% (13)	1.2% (303)	+0.018
Vitiligo	0.3% (3)	0.4% (104)	-0.015
Vitamin B12 deficiency	0.0% (0)	0.0% (2)	-0.013
Iron-deficiency anemia	8.8% (80)	9.1% (2261)	-0.012
Prior tofacitinib prescription	0.2% (2)	0.2% (43)	+0.010
Folate deficiency anemia	0.1% (1)	0.1% (36)	-0.010
Prior minoxidil prescription	0.2% (2)	0.2% (45)	+0.009
Protein-calorie malnutrition	3.0% (27)	2.9% (717)	+0.004
Stress or adjustment disorder	5.3% (48)	5.2% (1290)	+0.003
Folate deficiency	0.2% (2)	0.2% (58)	-0.003

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Vitamin B12 deficiency anemia	1.2% (11)	1.2% (297)	+0.001
Acute severe infection or hospitalization	4.1% (37)	4.1% (1009)	-0.000
Abnormal weight loss	0.0% (0)	0.0% (0)	
Bariatric surgery history	0.0% (0)	0.0% (0)	
Dermatology visit history	0.0% (0)	0.0% (0)	
Prior ritlecitinib prescription	0.0% (0)	0.0% (0)	
Prior deuruxolitinib prescription	0.0% (0)	0.0% (0)	

Hair-Loss-Directed Therapy Initiation

To corroborate the incident-alopecia findings with a treatment-based signal, we evaluated new initiation of hair-loss-directed therapies after index in the baseline-negative, repeat-prescription, five-covariate propensity-score–matched cohort of 12,863 patients per treatment arm (**Table 6**). Prescriptions were identified from the medication record and mapped by ingredient and brand name to a restricted, prespecified list of hair-regrowth agents: minoxidil, finasteride 1 mg (Propecia; the 1 mg hair-loss formulation, isolated by brand to exclude the 5 mg benign-prostatic-hyperplasia formulation), topical dutasteride, bimatoprost (Latisse), and the Janus kinase inhibitors tofacitinib, upadacitinib, baricitinib, ritlecitinib, and deuruxolitinib. A new starter was defined as a patient with at least one qualifying prescription in the 12 months after index (+1 to +365 days) and none in the 12 months before index (−365 to −1 days), and the proportion of new starters was compared between tirzepatide and semaglutide for each agent.

Positive- and Negative-Control Phenotype Analyses

As a positive-control benchmark for the AI-curated note pipeline — leveraging phenotypes with an established, directionally expected between-drug difference rather than an absence of expected association — note-based mentions of nausea, vomiting, diarrhea, fatigue, headache, and constipation were ascertained using the same extraction approach and confidence threshold within the five-covariate matched cohort, given established differential incretin-associated symptom profiles between tirzepatide and semaglutide. As a complementary true negative-control benchmark, 12-month incidence of ten phenotypes with no anticipated mechanistic relationship to GLP-1 pharmacology, weight loss, or alopecia (allergic rhinitis, hemorrhoids, inguinal hernia, impacted cerumen, benign melanocytic nevus, age-related cataract, actinic keratosis, carpal tunnel syndrome, sebaceous or epidermoid cyst, and deviated nasal septum) was ascertained from structured ICD-10-CM diagnoses in the same matched cohort. Both control analyses were prespecified as pipeline-validation contrasts and were not adjusted for multiplicity.

Index-Drug Brand Distribution

As a descriptive analysis, patients were classified by index-drug brand using the earliest brand-identified fill of the index ingredient. Tirzepatide brands were categorized as Mounjaro, Zepbound, or unspecified/other, and semaglutide brands as Ozempic, Wegovy, Rybelsus, or unspecified/other. Brand distributions were summarized in the unmatched repeat-prescription analytic cohort (**Table 11**), the five-covariate propensity-score matched cohort (**Table 12**), and the five-covariate plus achieved weight-loss-band matched cohort (**Table 13**). These brand-distribution analyses were descriptive and were not used to define the primary treatment arms or outcome comparisons. Denominators reflect patients with classifiable index-brand information and therefore may differ from the full analytic denominators used for the primary incident-alopecia analyses.

Table 11. Index-Drug Brand Distribution in the Unmatched Analytic Cohort. Shown is the distribution of the index brand among semaglutide and tirzepatide users in the unmatched baseline-negative analytic cohort (patients with at least two prescriptions). Each patient was classified by their index brand, defined as the brand of the earliest brand-identified prescription of the index drug; patients whose index-drug fills carried no mapped brand are shown as "Unspecified/other." Tirzepatide brands were Mounjaro and Zepbound; semaglutide brands

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were Ozempic, Wegovy, and Rybelsus. Values are the number of patients and the percentage of the treatment arm. Counts fewer than 11 are masked as "<11." The unmatched analytic cohort included 65,021 semaglutide users and 26,159 tirzepatide users.

Arm	Brand	Patients	% of arm	Arm N
Tirzepatide	Mounjaro	17894	68.4	26159
Tirzepatide	Zepbound	7789	29.8	26159
Tirzepatide	Unspecified/other	476	1.8	26159
Semaglutide	Ozempic	38722	59.6	65021
Semaglutide	Wegovy	16280	25.0	65021
Semaglutide	Rybelsus	4791	7.4	65021
Semaglutide	Unspecified/other	5228	8.0	65021

Table 12. Index-Drug Brand Distribution in the Five-Covariate Propensity-Score Matched Cohort. Shown is the distribution of the index brand among semaglutide and tirzepatide users in the five-covariate propensity-score (PS-5) matched cohort (matched 1:1 on age, race, sex, baseline body-mass index, and type 2 diabetes). Each patient was classified by their index brand, defined as the brand of the earliest brand-identified prescription of the index drug; patients whose index-drug fills carried no mapped brand are shown as "Unspecified/other." Tirzepatide brands were Mounjaro and Zepbound; semaglutide brands were Ozempic, Wegovy, and Rybelsus. Values are the number of patients and the percentage of the treatment arm. Counts fewer than 11 are masked as "<11." The PS-5 matched cohort included 12,863 semaglutide users and 12,863 tirzepatide users.

Arm	Brand	Patients	% of arm	Arm N
Tirzepatide	Mounjaro	6783	52.7	12863
Tirzepatide	Zepbound	5747	44.7	12863
Tirzepatide	Unspecified/other	333	2.6	12863
Semaglutide	Ozempic	5287	41.1	12863
Semaglutide	Wegovy	5785	45.0	12863
Semaglutide	Rybelsus	387	3.0	12863
Semaglutide	Unspecified/other	1404	10.9	12863

Table 13. Index-Drug Brand Distribution in the Propensity-Score Matched Cohort with Additional Balance on Achieved Weight-Loss Band. Shown is the distribution of the index brand among semaglutide and tirzepatide users in the propensity-score matched cohort additionally balanced on achieved weight-loss band (PS-5 plus weight-loss band, "PS-6"). Each patient was classified by their index brand, defined as the brand of the earliest brand-identified prescription of the index drug; patients whose index-drug fills carried no mapped brand are shown as "Unspecified/other." Tirzepatide brands were Mounjaro and Zepbound; semaglutide brands were Ozempic, Wegovy, and Rybelsus. Values are the number of patients and the percentage of the treatment arm. Counts fewer than 11 are masked as "<11." The matched cohort included 11,046 semaglutide users and 11,046 tirzepatide users.

Arm	Brand	Patients	% of arm	Arm N
Tirzepatide	Mounjaro	5845	52.9	11046
Tirzepatide	Zepbound	4896	44.3	11046
Tirzepatide	Unspecified/other	305	2.8	11046
Semaglutide	Ozempic	4543	41.1	11046
Semaglutide	Wegovy	5048	45.7	11046
Semaglutide	Rybelsus	306	2.8	11046
Semaglutide	Unspecified/other	1149	10.4	11046

Single-Cell Receptor Expression Analysis Using CELLxGENE Census

To identify potential cellular targets of incretin signaling in alopecia-relevant tissues, we analyzed publicly available human single-cell RNA-sequencing data from the CELLxGENE Census (https://cellxgene.cziscience.com/). All annotated human skin and scalp datasets available in the Census at the time of analysis were queried. Cells were grouped according to the harmonized

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CELLxGENE cell-type annotations and tissue of origin, and tissue-cell pairs relevant to skin, scalp, hair follicle, immune, stromal, and vascular compartments were evaluated. Expression of GIPR and GLP1R was quantified independently within each tissue-cell pair.

Statistical Methods

Between-arm comparisons of incident alopecia and of hair-loss-therapy initiation were summarized as the relative risk (RR), computed as the incidence proportion in tirzepatide users divided by that in semaglutide users, with 95% confidence intervals (CIs) derived from the log risk-ratio (Katz) standard error [21], and two-sided P values for each 2×2 comparison obtained from the Pearson chi-square test (equivalently, the two-proportion z test). Within-arm incidence proportions are additionally reported with Wilson 95% CIs; continuous baseline variables are summarized as mean (standard deviation) and compared using the SMD (absolute SMD of at least 0.1 indicating imbalance), and binary variables as counts (percentages). For developer-versus-non-developer analyses, SMDs were calculated with developers as the reference numerator and were interpreted descriptively. Paired laboratory changes were summarized with Cohen's d based on the distribution of within-patient post-minus-pre differences; no between-treatment causal inference was assigned to these laboratory comparisons. Pooled estimates across contributing sources were obtained by summing the corresponding 2×2 tables before computing the RR, CI, and test statistic. The pooled 12-month incident-alopecia RR was the prespecified primary contrast; stratified, subgroup, and ICD-coded subtype comparisons are presented without adjustment for multiplicity and, where event counts were small, are interpreted as exploratory. The paired laboratory and baseline-feature analyses were also considered exploratory and were not adjusted for multiplicity. To comply with data-use privacy requirements, any cell with fewer than 11 patients or events is reported as "<11."

Statistical Analysis Plan for Study Advancement

The analytic approach followed established pharmacoepidemiologic and biostatistical convention throughout: the incident-user, active-comparator cohort design is the standard real-world-evidence paradigm for drug-effect estimation from routinely-collected EHR data and was reported per the STROBE and RECORD frameworks [10,11], with a within-class active comparator (semaglutide) chosen to limit confounding by indication [12,13]. Propensity scores estimated by logistic regression with 1:1 greedy nearest-neighbor matching within a 0.2-standard-deviation caliper on the logit, and balance assessed by SMDs, follow established causal-inference methodology [14–16], while the additional weight-loss-band matched cohort implements a weight-loss-balanced sensitivity analysis assessing whether the between-drug difference persisted after balancing the magnitude of achieved weight loss. Alopecia and baseline conditions were ascertained from structured codes and from clinical notes using a validated NLP extraction pipeline, consistent with evidence that support clinical phenotyping from notes at expert-comparable accuracy [22]. Incident events were counted only among at-risk, alopecia-free patients over a window beginning 7 days after index, and RRs with chi-square tests and stratified within-band comparisons used standard estimators [21]; immortal-time and reverse-causation concerns were addressed through incident-event restriction, baseline exclusion of prevalent alopecia, and the minimum exposure-to-event latency, mirroring recognized corrections for time-related bias [23], and because observed follow-up was shorter in the tirzepatide arm, a direction of imbalance that biases against detecting excess alopecia in that arm, the primary contrast was interpreted as conservative. All patients had evidence of EHR activity at or beyond 12 months, and the primary endpoint was restricted to the common 7-to-365-day risk window; therefore, differences in total observed follow-up beyond 12 months were not used to define the primary risk period.

Institutional Review Board Statement, Informed Consent Statement, De-Identification and HIPAA Compliance Certification

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Prior to analysis, all EHR data were de-identified under an expert determination consistent with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR §164.514(b)(1)). The de-identification methodology [24,25] employed a multi-layered transformation approach to both structured and unstructured data fields. In structured data, direct identifiers including patient names and precise geographic locations were excluded entirely, while indirect identifiers underwent specific transformations: patient identifiers, medical record numbers, and accession numbers were replaced with one-way cryptographic hashes using confidential salts to preserve linkage across patient encounters; all dates were shifted backward by patient-specific random offsets (1 to 31 days) to preserve temporal relationships while obscuring exact event timing; ZIP codes were truncated to two-digit state-level resolution; and continuous variables including age, height, weight, and body mass index were thresholded to prevent identification of extreme values (for example, ages 89 years or older transformed to '89+' and BMI over 40 transformed to '40+'). In clinical text, an ensemble de-identification system that combines attention-based deep learning with rule-based methods achieved an estimated >99% recall for personally identifiable information (PII) detection, with detected identifiers replaced by plausible fictional surrogates. Institutional Review Board Statement and Informed Consent Statement are not applicable.

Data Harmonization

To address heterogeneity in EHR data, we harmonized clinical variables including medications, anthropometric measurements, and diagnoses to standardized concepts. For medications, we first constructed a standardized drug concept database combining the nference knowledge graph with RxNorm hierarchies to capture ingredient, brand, and dose-specific information. Medication records were matched using a hierarchical approach prioritizing RxNorm codes when available, followed by ingredient-level matching, and finally natural language processing and pattern matching on free-text medication orders when structured codes were absent. For anthropometric measurements (height, weight, body mass index), we created a unified vocabulary from SNOMED and LOINC and matched EHR measurement descriptions using standardized text matching algorithms with abbreviation expansion and synonym resolution; ambiguous mappings were resolved using OpenAI GPT-4o with summary statistics as context, followed by manual verification. For diagnoses, we developed a hierarchical disease concept database from the knowledge graph and matched EHR diagnosis records by identifying the most specific common child concept in the hierarchy.

Results

Characterization of Study Cohorts

There were 26,159 patients with at least two tirzepatide prescriptions who had no pre-existing diagnosis of alopecia and met the other study inclusion criteria (see **Methods**), and there were 65,021 such patients with at least two semaglutide prescriptions. These cohorts showed a number of differences in demographic and baseline clinical characteristics (**Table 1**), with the tirzepatide cohort showing a lower average age (52.1 versus 54.3 years; standardized mean difference [SMD] -0.17), higher percentage of females (64.5% versus 61.8%), and higher prevalence of type 2 diabetes (11.1% versus 8.8%; SMD 0.08), although mean baseline HbA1c was slightly higher in the semaglutide cohort (7.1% versus 6.7%; SMD -0.18). Obesity diagnosis was present in 81% and 79% of the tirzepatide and semaglutide cohorts at baseline (SMD 0.04), and average BMI was 36.2 kg/m^2 in both groups.

After 1-to-1 propensity-score matching on age, sex, race, BMI, type 2 diabetes status, there were 12,863 patients in the primary matched tirzepatide and semaglutide cohorts (**Table 1**). Matching significantly improved cohort balance, with a mean age of 50.7 years in both groups (SMD 0.00), type 2 diabetes diagnosis in 20.6% of the tirzepatide cohort and 19.9% of the semaglutide cohort (SMD 0.02), and mean baseline HbA1c values of 6.0% and 6.1% (SMD -0.08). Baseline BMI was 36.2 kg/m^2 in the tirzepatide cohort and 36.3 kg/m^2 in the semaglutide cohort (SMD -0.02).

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Given that alopecia in the setting of incretin therapy has been partially attributed to weight loss itself, we also constructed propensity-matched tirzepatide and semaglutide cohorts (N = 11,046) that were matched on weight loss magnitude during the one-year period after initial prescription, in addition to the other variables listed above. These cohorts were similarly well-balanced, with nearly identical baseline characteristics compared to the primary propensity-matched cohorts (**Table 2**).

Alopecia Incidence and Initiation of Hair Loss Therapies Was Higher Among Tirzepatide Users than Semaglutide Users

In the unmatched cohorts, the incidence of alopecia was significantly higher after initiation of tirzepatide compared to semaglutide (3.73% versus 2.80%; RR, 1.33; 95% CI, 1.23 to 1.44; P<0.001) **(Figure 1, Table 5**). In the propensity-matched cohorts, new diagnosis of alopecia within one year following the first prescription occurred in 540 of 12,863 (4.20%) tirzepatide users versus 371 of 12,863 (2.88%) semaglutide users (RR 1.46; 95% CI 1.28-1.66; P<0.001) **(Table 5**). This trend of higher alopecia incidence after tirzepatide initiation compared to semaglutide initiation was recapitulated in a time-to-event analysis (hazard ratio [HR] 1.46, 95% CI 1.28-1.67, p<0.001; **Figure 4**), with divergence of the alopecia cumulative incidence curves beginning at approximately 6 months (1.55% versus 1.24%) after the first prescription and increasing through the 12-month follow-up period (4.20% versus 2.88%).

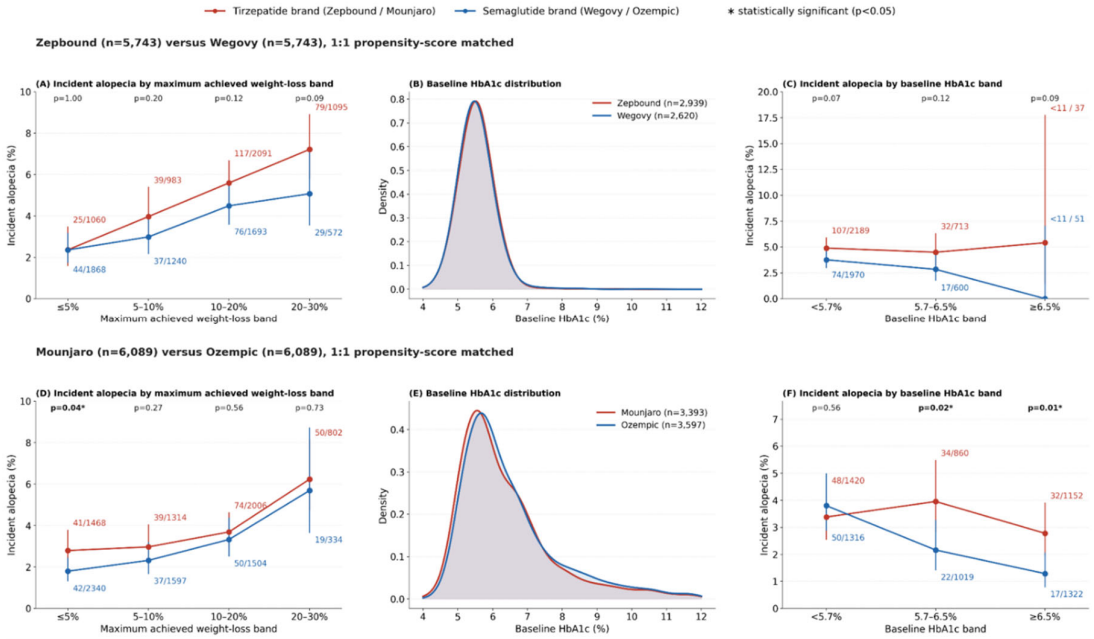

Figure 3. Brand-specific matched analyses of incident alopecia after tirzepatide versus semaglutide products. Shown are 12-month incident new-onset alopecia rates in brand-specific 1:1 propensity-score matched cohorts balanced on age, race, sex, baseline body-mass index, and type 2 diabetes. Panels A through C compare Zepbound with Wegovy, with 5,743 patients in each arm; Panels D through F compare Mounjaro with Ozempic, with 6,089 patients in each arm. Panels A and D show incident alopecia by maximum achieved weight-loss band. Panels B and E show the baseline HbA1c distributions among patients with available baseline HbA1c measurements. Panels C and F show incident alopecia by baseline HbA1c band. Points indicate observed incidence percentages, vertical bars indicate 95% confidence intervals, and labels show the number of incident alopecia cases over the number of patients at risk. Counts fewer than 11 are masked as "<11." Asterisks indicate statistically significant between-group differences at P<0.05. Red denotes tirzepatide-brand products, Zepbound or Mounjaro, and blue denotes semaglutide-brand products, Wegovy or Ozempic.

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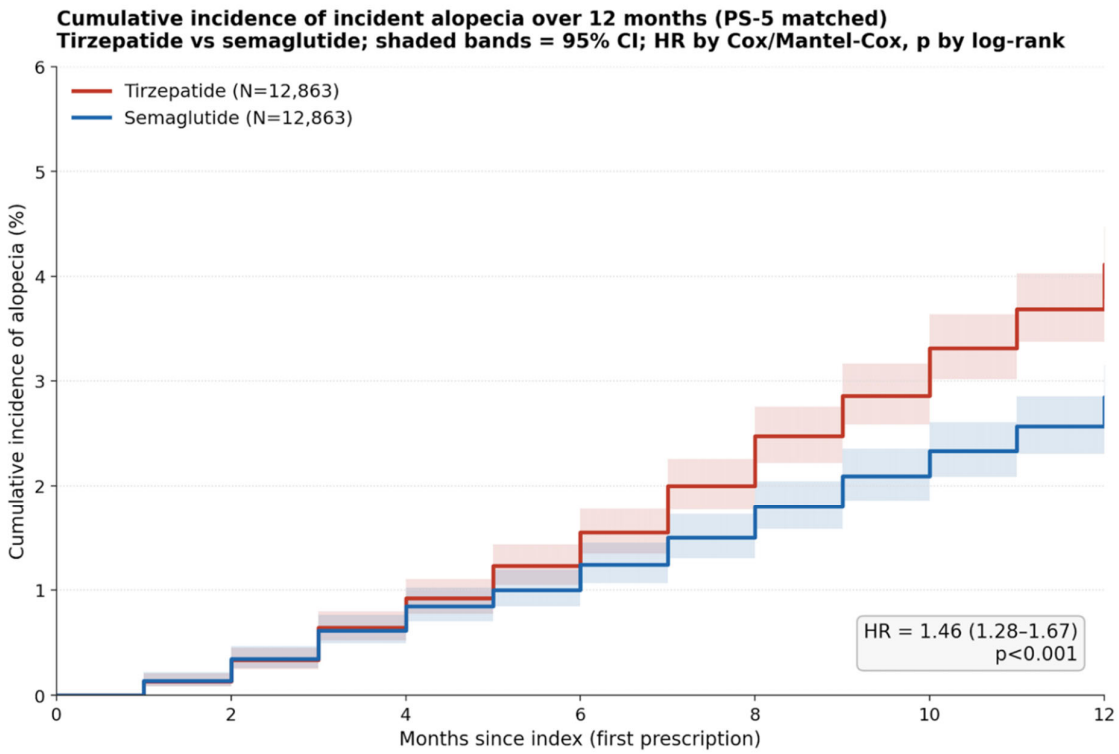

Figure 4. Cumulative Incidence of Incident Alopecia in the Propensity-Score Matched Cohort. Shown is the cumulative first-event incidence of incident new-onset alopecia over the 12-month observation window among tirzepatide and semaglutide users in the five-covariate propensity-score matched cohort (12,863 per arm); shaded bands are 95% Wilson confidence intervals. The curves were similar early after index and separated progressively after approximately month 5. The hazard ratio (Mantel–Cox) and log-rank P value are annotated. Red denotes tirzepatide and blue denotes semaglutide.

A complementary assessment of hair loss therapy initiation corroborated these observations. In the propensity-matched cohorts (N=12,863 each), the baseline prevalence of prescriptions for hair loss-related therapies was well-balanced (**Table 1**). However, minoxidil initiation occurred more frequently in the tirzepatide cohort (0.41% versus 0.20%; RR 2.04; 95% CI 1.28-3.26; P=0.002) (**Figure 8**). Bimatoprost showed a directionally consistent trend that did not reach statistical significance (0.21% versus 0.13%; RR 1.59; 95% CI 0.87-2.91; P=0.13). At baseline, fewer than 11 patients in each cohort had a prior minoxidil prescription (tirzepatide: <11; semaglutide: <11), whereas prior bimatoprost prescriptions were present in 27 tirzepatide-treated patients versus 11 semaglutide-treated patients. Other hair loss-related therapies did not significantly differ in their use after tirzepatide or semaglutide initiation or had an inadequate number of incident events to support analysis (**Table 6**).

To contextualize these observations, we assessed both positive and negative control outcomes following tirzepatide or semaglutide initiation. Several positive control outcomes (well-established adverse effects of incretin therapies) showed slightly lower rates in the tirzepatide cohort (**Figure 10**), including nausea (43.7% versus 46.1%; RR 0.95, 95% CI 0.92-0.97), vomiting (18.0% versus 20.9%; RR 0.86, 95% CI 0.82-0.90), diarrhea (22.4% versus 23.8%; RR 0.94, 95% CI 0.90-0.98), and fatigue (35.0% versus 38.8%; RR 0.90, 95% CI 0.87-0.93). These findings indicate that the observed higher incidence of alopecia is unlikely to be an artifact of greater overall documentation of adverse events after initiation of tirzepatide compared to semaglutide. On the other hand, multiple negative control outcomes (phenotypes with no plausible mechanistic relationship to GLP-1 receptor pharmacology, weight loss, or alopecia) showed no significant difference between the tirzepatide and semaglutide cohorts (**Figure 11**), including allergic rhinitis (2.82% vs. 3.19%; RR, 0.88; 95% CI, 0.73–1.04),

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hemorrhoids (1.71% vs. 1.54%; RR, 1.11; 95% CI, 0.89–1.38), benign melanocytic nevus (1.52% vs. 1.52%; RR, 1.00; 95% CI, 0.81–1.26), age-related cataract (0.45% vs. 0.63%; RR, 0.71; 95% CI, 0.52–1.06), actinic keratosis (0.61% vs. 0.45%; RR, 1.35; 95% CI, 0.95–1.97), and carpal tunnel syndrome (0.86% vs. 0.96%; RR, 0.90; 95% CI, 0.67–1.18).

Alopecia Incidence Correlated with Weight Loss Magnitude and Was Higher After Tirzepatide than Semaglutide Across Weight Loss Strata

In the primary propensity-score matched cohort (N = 12,863 each), incident alopecia increased monotonically with the magnitude of achieved weight loss in both treatment groups (**Figure 2A**). Among tirzepatide users, 12-month cumulative incident alopecia rose from 2.5% at ≤5% weight loss to 3.4% at 5 to 10%, 4.6% at 10 to 20% and 6.9% at 20 to 30%; among semaglutide users, the corresponding cumulative incidence increased from 2.0% to 2.8%, 3.8% and 4.8% across the same bands. When performing comparisons within each stratum of achieved weight loss, alopecia incidence was significantly higher in the tirzepatide than semaglutide cohort among patients with 20-30% weight loss (6.9% vs. 4.8%; RR, 1.44; P=0.027). The lower weight loss strata showed directionally consistent but not statistically significant differences, including in patients with ≤5% weight loss (2.5% vs. 2.0%; RR 1.23, P=0.18), 5 to 10% weight loss (3.4% vs. 2.8%; RR 1.23, P=0.18), and 10 to 20% weight loss(4.6% vs. 3.8%; RR 1.21, P=0.078).

Alopecia Incidence Was Higher Among Tirzepatide Users than Semaglutide Users After Matching for Achieved Weight Loss

To more directly assess whether the higher alopecia incidence after tirzepatide initiation was due to its greater associated weight loss, we analyzed the secondary cohort which was additionally matched on achieved weight loss magnitude (N = 11,046 per arm). In these cohorts, the 12-month cumulative incidence of alopecia was again higher after initiation of tirzepatide than semaglutide (4.24% vs. 3.33%; RR, 1.27; 95% CI, 1.11 to 1.45; P<0.001) (**Table 5**). This difference was directionally consistent across the matched strata and reached statistical significance in the ≤5% weight loss group (2.5% vs. 1.6%; RR 1.53; P=0.023) and the 10 to 20% weight loss group (4.6% vs. 3.6%; RR 1.29; P=0.019), with a similar trend seen in the 20 to 30% band (7.3% vs. 5.5%; RR 1.31; P=0.050).

Demographic and Clinical Enrichments Among Patients with Incident Alopecia After Starting Incretin Therapy

To identify potential risk factors for alopecia associated with incretin therapy, we compared baseline demographic and clinical features between patients who did versus did not develop alopecia in the primary propensity-matched cohorts (**Figure 9**, **Tables 8-10**). In the pooled cohort of patients who initiated tirzepatide or semaglutide which included 911 patients who developed alopecia and 24,815 patients who did not, the strongest enrichment was for female sex (89.5% versus 69.3%; SMD 0.51). Other enriched features among alopecia developers included hypothyroidism (29.1% versus 22.0%; SMD: 0.16), lower baseline HbA1c (5.8% versus 6.0%; SMD: -0.22), and lower baseline weight (101.3 kg versus 106.2 kg; SMD: -0.21), suggesting that developers were not characterized by greater baseline metabolic burden.

Similar patterns were seen in the cohorts of each individual medication. In the tirzepatide cohort (540 alopecia developers and 12,323 non-developers) (**Table 8**), the strongest enrichment was again female sex (90.6% versus 68.9%; SMD: 0.56). Other enrichments included hypothyroidism (28.1% versus 21.6%; SMD: 0.15) and multiple reproductive-endocrine phenotypes including menstrual irregularity or amenorrhea (20.0% versus 13.9%; SMD: 0.17) and polycystic ovarian syndrome (6.7% versus 3.6%; SMD: 0.14). As was seen in the overall cohort, tirzepatide users who developed alopecia had lower baseline weight (100.8 kg versus 106.5 kg; SMD: -0.25) and lower HbA1c (5.8% versus 6.0%; SMD: -0.18).

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In the semaglutide cohort (371 alopecia developers and 12,492 non-developers) (**Table 9**), female sex (87.9% versus 69.7%; SMD: 0.46), hypothyroidism (30.5% versus 22.3%; SMD: 0.19), lower baseline HbA1c (5.8% versus 6.1%; SMD: -0.25), and lower weight (102.1 kg versus 105.8 kg; SMD: -0.16) were again enriched among alopecia developers. Additional differential phenotypes included higher rates of rheumatoid arthritis among developers (6.2% versus 3.0%; SMD: 0.15) and lower rates of hyperlipidemia (48.2% versus 57.5%; SMD: -0.19) and atherosclerotic cardiovascular disease (8.9% versus 13.9%; SMD: -0.16).

Differential Alopecia Incidence Between the Tirzepatide and Semaglutide Cohorts Is Most Pronounced in Patients with Higher Baseline HbA1c and Moderate Treatment-Associated HbA1c Reduction

To determine whether differential alopecia incidence was related to baseline glycemic control or treatment-associated changes in glycemic control, we next performed multiple stratified analyses. Across baseline HbA1c strata (<5.7%, 5.7-6.5%, ≥6.5%), tirzepatide had significantly higher incident alopecia than semaglutide in all three strata, with the strength of the association increasing at higher baseline HbA1c: 4.3% versus 3.4% in the <5.7% group (RR 1.25, P=0.049), 3.9% versus 2.3% in the 5.7-6.5% group (RR 1.69, P=0.007), and 2.9% versus 1.5% in the ≥6.5% group (RR 1.99, P=0.011) (**Figure 2B**; counts and denominators in Supplementary Table **S1**). Interestingly, when stratified instead by change in HbA1c between the pre- and post-treatment periods, alopecia incidence was only significantly different among patients with a 0-0.5% reduction (5.0% for tirzepatide versus 3.0% for semaglutide; RR 1.64, P=0.005) or a 0.5-1.0% reduction (5.4% versus 2.5%; RR 2.16, P=0.006) (**Figure 2C**; counts and denominators in **Supplementary Table S1**). Alopecia was seen at similar rates in patients who showed no change or an increase in HbA1c (3.8% [32/846] versus 2.6% [27/1044]; RR 1.46, P=0.14) and in patients with a reduction of more than 1.0% (2.8% [22/787] versus 2.6% [18/692]; RR 1.07, P=0.82).

Tirzepatide Is Associated with Higher Alopecia Incidence Among Patients Who Reach Lower or Higher Maximum Dose Levels

We next assessed the incidence of alopecia in the primary matched cohorts stratified by their maximum dose achieved during the 12-month observation period (**Figure 2D**). Among patients who reached only a lower maximum dose (<10 mg weekly for tirzepatide; <1.0 mg weekly for semaglutide), alopecia occurred in 255 of 6671 tirzepatide users (3.8%) versus 104 of 4785 semaglutide users (2.2%; RR 1.76; P<0.001). Among patients who reached a higher maximum dose (≥10 mg weekly for tirzepatide; ≥1.0 mg for semaglutide), alopecia occurred in 284 of 6187 tirzepatide users (4.6%) versus 267 of 8068 semaglutide users (3.3%; RR 1.39; P<0.001).

In the secondary matched cohorts (additionally matched on weight loss magnitude), tirzepatide was also associated with higher incident alopecia in both the lower maximum dose strata (3.9% vs. 2.8%; RR 1.40; P=0.004) and the higher maximum dose strata (4.6% vs. 3.6%; RR 1.28; P=0.005) (**Figure 5B**).

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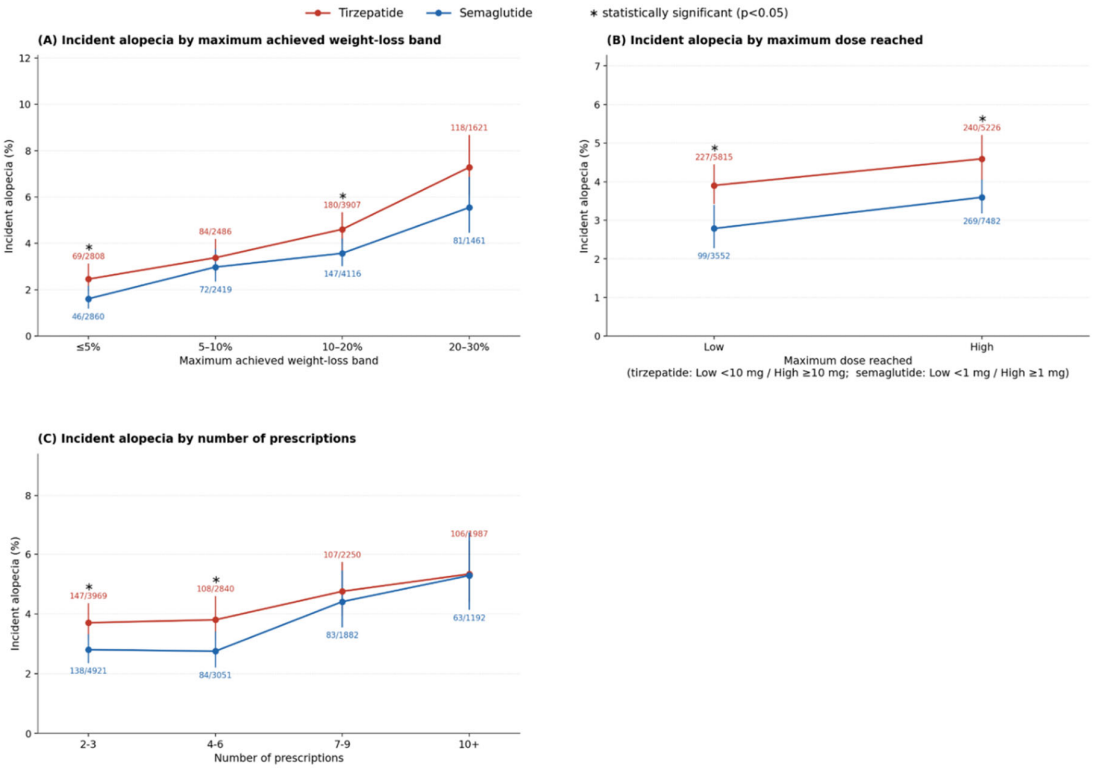
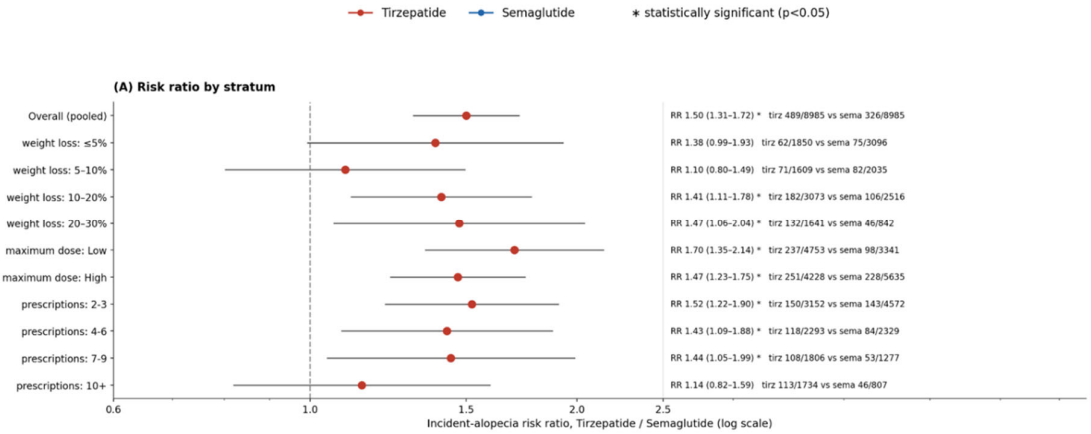


Figure 5. Incident Alopecia after Additional Matching on Achieved Weight-Loss Band. Shown are 12-month rates of incident new-onset alopecia among tirzepatide and semaglutide users in the propensity-score matched cohort additionally balanced on achieved weight-loss band. Panel A shows incident alopecia by maximum achieved weight-loss band; Panel B, by maximum dose reached; and Panel C, by number of prescriptions. Points indicate observed incidence percentages, vertical bars indicate 95% confidence intervals, and labels show the number of incident alopecia cases over the number of patients at risk; counts fewer than 11 are shown as "<11." Asterisks indicate statistically significant between-group differences at P<0.05. Across the pooled weight-loss-band matched cohort, tirzepatide remained associated with higher incident alopecia than semaglutide (RR, 1.27; 95% CI, 1.11 to 1.45; P<0.001). HbA1c denotes glycated hemoglobin.



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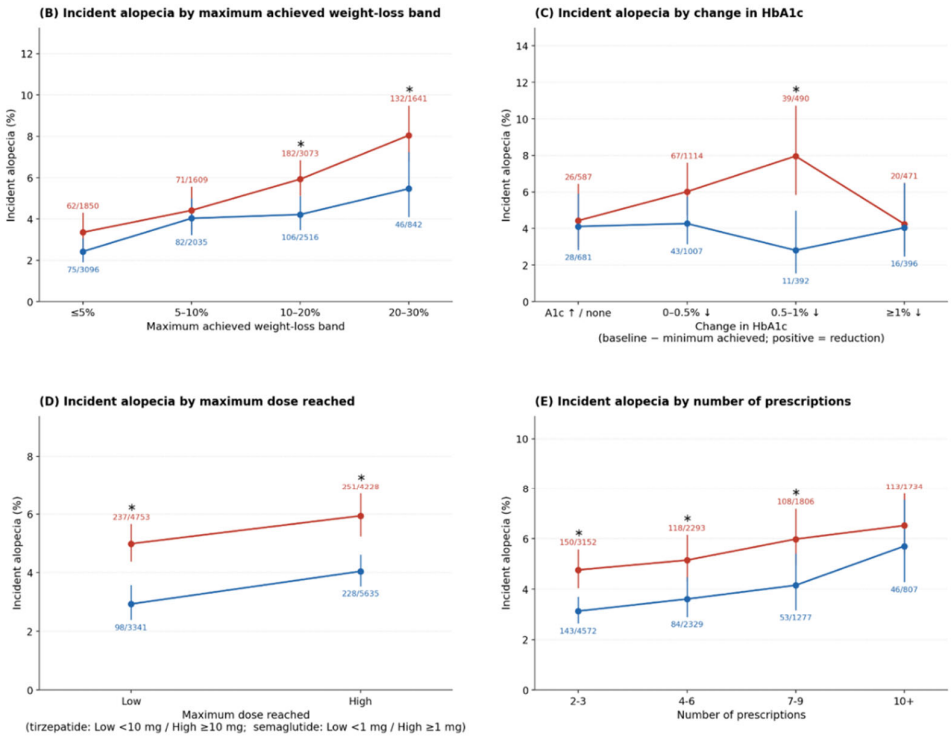

Figure 6. Incident Alopecia among Female Patients with Two or More Prescriptions of Tirzepatide versus Semaglutide. Shown are 12-month rates and risk ratios for incident new-onset alopecia among female patients in the five-covariate propensity-score matched cohort with two or more prescriptions. **Panel A** shows tirzepatide-versus-semaglutide risk ratios across the pooled female cohort and across strata defined by achieved weight loss, maximum dose reached, and prescription count; points indicate risk ratios, horizontal bars indicate 95% confidence intervals, and the dashed vertical line denotes no difference between treatments. **Panel B** shows incident alopecia by maximum achieved weight-loss band. **Panel C** shows incident alopecia by change in HbA1c (baseline minus the minimum achieved value; positive values indicate a reduction). **Panel D** shows incident alopecia by maximum dose reached. **Panel E** shows incident alopecia by number of prescriptions. In Panels B through E, points indicate observed incidence percentages, vertical bars indicate 95% confidence intervals, and labels show the number of incident alopecia cases over the number of patients at risk. Asterisks indicate significant tirzepatide-versus-semaglutide differences at P<0.05. Across the pooled female matched cohort, incident alopecia occurred in 489 of 8985 tirzepatide users (5.44%) and 326 of 8985 semaglutide users (3.63%), corresponding to a risk ratio of 1.50 (95% CI, 1.31-1.72; P<0.001).

Alopecia Incidence Increases with Higher Numbers of Incretin Therapy Prescriptions

We next assessed the relationship between alopecia incidence and incretin therapy prescription counts (a potential proxy for treatment exposure). In both the semaglutide and tirzepatide groups, the cumulative incidence of alopecia increased monotonically across prescription count buckets in the primary matched cohorts (**Figure 2E**). Further, the percentage of patients with new alopecia after treatment initiation was higher for tirzepatide than semaglutide across all prescription-count strata, with statistically significant differences observed in the 2 to 3 and 4 to 6 prescription buckets. Specifically, among patients with 2 to 3 prescriptions, new-onset alopecia occurred in 3.6% tirzepatide users and 2.7% of semaglutide users (RR 1.33; P=0.008). Among those with 4 to 6 prescriptions, incident alopecia was documented in 3.9% versus 2.4% (RR 1.65; P<0.001). These values were 4.7% versus 3.5% (RR 1.33; P = 0.051) and 5.1% versus 4.2% (RR 1.20; P=0.27) for the groups with 7 to 9 and at least 10 prescriptions, respectively.

In a mirrored analysis of the secondary matched cohorts (additionally matched on weight loss magnitude), tirzepatide was again significantly associated with higher incident alopecia in the lower

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prescription-count strata, including in patients with 2 to 3 prescriptions (3.7% vs. 2.8%; RR 1.32; P=0.017) or 4 to 6 prescriptions (3.8% vs. 2.8%; RR 1.38; P=0.023).

Age- and Sex-Stratified Analyses Demonstrate Similar Patterns of Alopecia Incidence After Initiation of Tirzepatide Versus Semaglutide

When the primary propensity-matched cohorts were stratified into subsets of young, middle aged, and older adults, tirzepatide was associated with higher cumulative incidence of alopecia in each age stratum (**Figure 7A and 7B**). Among patients 18 to 34 years of age, alopecia occurred in 4.56% versus 3.15% of tirzepatide and semaglutide initiators, respectively (RR 1.45, P=0.046). The corresponding values were 4.22% versus 2.88% among patients 35 to 64 years of age (RR 1.46; P<0.001) and 3.85% versus 2.33% among those 65 years and older (RR 1.65; P=0.006).

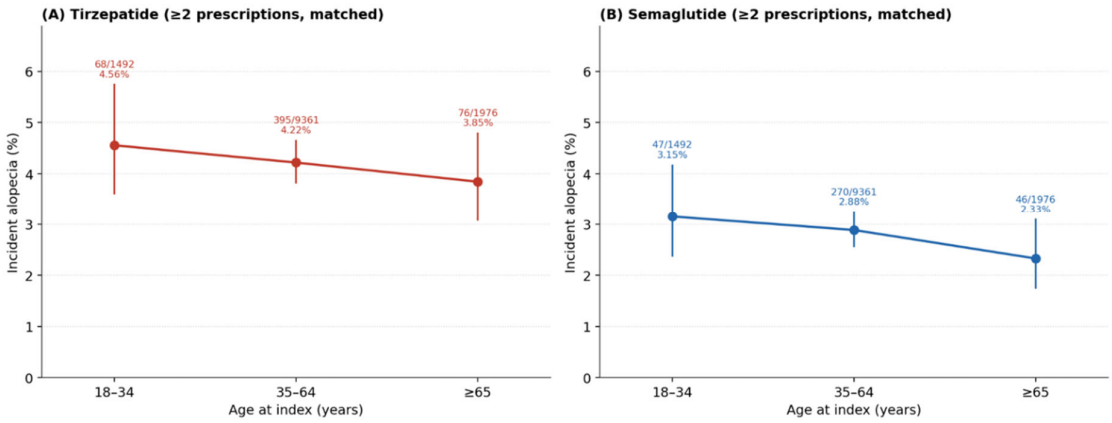

Figure 7. Incident Alopecia by Age among Propensity-Score-Matched Patients with Two or More Prescriptions of (A) Tirzepatide or (B) Semaglutide. Shown are 12-month rates of incident new-onset alopecia by adult age group. Within each pair, the left panel (A) shows tirzepatide users and the right panel (B) shows semaglutide users. Points indicate observed incidence percentages, vertical bars indicate 95% confidence intervals, and labels show the number of incident alopecia cases over the number of patients at risk with corresponding percentages. Analyses are restricted to adults; patients younger than 18 years are not displayed.

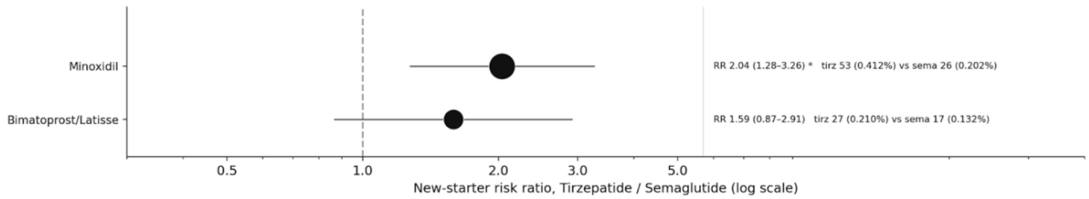

Figure 8. New starts of hair-loss-directed therapies after Tirzepatide versus Semaglutide initiation in propensity-score matched cohorts. Shown are post-index new-starter risk ratios for hair-loss-directed therapies among baseline-negative cohorts in the 1:1 five-covariate propensity-score (PS-5) matched cohorts (12,863 patients per arm). Points indicate the tirzepatide-versus-semaglutide new-starter risk ratio for each therapy, horizontal bars indicate 95% confidence intervals, and the dashed vertical line denotes no difference between groups. Dot size is proportional to the total number of new starters across both groups. Values greater than 1.0 favor higher new-start frequency after tirzepatide. Agents with fewer than 20 total new starters are not shown, and counts fewer than 11 are shown as "<11." Asterisks indicate statistical significance at P<0.05.

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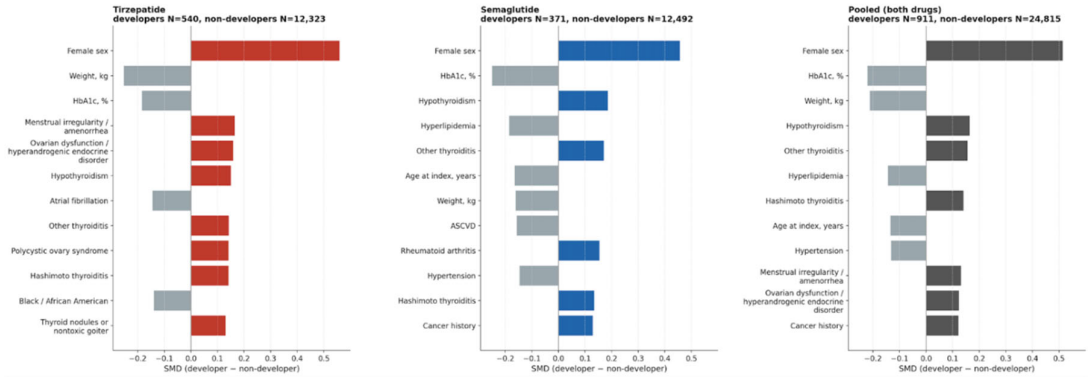

Figure 9. Baseline Features Enriched among Incident-Alopecia Developers versus Non-Developers within Each Treatment Arm and in the Pooled Cohort. Shown are standardized mean differences for baseline features comparing patients who developed incident alopecia with those who did not, evaluated separately within the five-covariate propensity-score matched tirzepatide and semaglutide cohorts and in the pooled cohort of both drugs. The left panel shows tirzepatide users, including 540 incident-alopecia developers and 12,323 non-developers; the middle panel shows semaglutide users, including 371 developers and 12,492 non-developers; and the right panel shows the pooled cohort, including 911 developers and 24,815 non-developers. Alopecia and hair-loss diagnoses (the study outcome and its subtypes) were excluded from this analysis, as they represent the outcome rather than baseline determinants. Positive standardized mean differences indicate features that were more prevalent or higher among patients who developed alopecia, whereas negative values indicate features that were lower among developers. Among tirzepatide users, incident alopecia was most strongly enriched among female patients and was also associated with menstrual irregularity or amenorrhea, ovarian dysfunction or hyperandrogenic endocrine disorder, hypothyroidism, thyroiditis, Hashimoto thyroiditis, and polycystic ovary syndrome. Among semaglutide users, developers were similarly enriched for female sex, hypothyroidism, thyroiditis, Hashimoto thyroiditis, and rheumatoid arthritis. In the pooled cohort, developers were most enriched for female sex, hypothyroidism, thyroiditis, Hashimoto thyroiditis, menstrual irregularity or amenorrhea, and ovarian dysfunction or hyperandrogenic endocrine disorder. In all arms, alopecia developers tended to have lower baseline cardiometabolic burden, including lower weight, HbA1c, age, ASCVD, or hyperlipidemia depending on the treatment arm. SMD denotes standardized mean difference; PS-5, propensity-score matching on age, race, sex, baseline body-mass index, and type 2 diabetes.

Given that the majority of patients who had a new diagnosis of alopecia after initiating an incretin therapy were female, we also performed subanalyses on female patients in the matched cohorts. In the primary matched cohorts (without matching on weight loss magnitude), tirzepatide was associated with a significantly higher 12-month cumulative incidence of alopecia than semaglutide (5.44% versus 3.63%; RR 1.50, 95% CI 1.31-1.72; P<0.001) (**Figure 6A**). As was observed for the overall cohorts, the 12-month cumulative incidence of alopecia increased monotonically with greater achieved weight loss among females (**Figure 6B**), for example rising from 3.4% at ≤5% weight loss to 8.0% at 20-30% weight loss for tirzepatide and from 2.4% at ≤5% weight loss to 5.5% at 20-30% weight loss for semaglutide.

Within the female cohort, stratified by achieved weight loss, alopecia incidence was significantly higher after tirzepatide initiation in the 10-20% weight loss group (5.92% versus 4.21%; RR 1.41, 95% CI 1.11-1.78; P=0.004) and the 20-30% weight loss group (8.04% versus 5.46%; RR 1.47, 95% CI 1.06-2.04; P=0.018) (**Figure 6B**). Of note, the difference in alopecia incidence for the 10-20% weight loss group was not statistically significant in the overall (male and female) cohort (RR 1.21, P=0.078), indicating that this signal in patients with moderate weight loss may be specific to females. There was no statistically significant difference in alopecia incidence between tirzepatide and semaglutide when comparing the ≤5%, 5-10%, and 30-40% weight loss groups.

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Other analyses on the female subset also mirrored the findings observed in the overall cohort. For example, the largest magnitude difference in alopecia incidence was seen in patients with a 0.5 to 1.0% reduction in HbA1c (7.96% for tirzepatide versus 2.81% for semaglutide; RR 2.84, 95% CI 1.47–5.46; P=0.001) (**Figure 6C**). Further, higher incidence of hair loss was seen in tirzepatide compared to semaglutide for patients who reached either a low maximum dose (4.99% versus 2.93%; RR 1.70, 95% CI 1.35-2.14; P<0.001) or a high maximum dose (5.94% versus 4.05%; RR 1.47; 95% CI 1.23-1.75; P<0.001) (**Figure 6D**). Finally, an exposure gradient (using prescription count as a proxy for treatment exposure) was seen in females which was comparable to the overall population, again with significantly higher rates in the tirzepatide cohort compared to the semaglutide cohort within each prescription count stratum (**Figure 6E**).

Repeated Laboratory Measurements Do Not Identify Nutrient Depletion Among Patients Who Develop Alopecia After Initiation of Tirzepatide or Semaglutide

Among patients in the primary matched cohorts who developed incident alopecia and had paired pre-index and post-index laboratory values available, there was no evidence of significant vitamin or mineral depletion after treatment initiation (**Table 7A and 7B**). Ferritin, which partly reflects total body iron stores, showed modest increases between the pre- and post-treatment periods for both tirzepatide (mean 100.3 versus 147.0; d: 0.31; N = 42) and semaglutide (mean 69.9 versus 134.8; d: 0.21; N = 34). Mean serum iron showed a non-significant reduction in the tirzepatide cohort (76.0 versus 73.2; d: -0.08; N = 25) but a slight increase in the semaglutide cohort (62.0 versus 71.6; d: 0.26; N=24). Vitamin B12 and folate did not show meaningful changes, with both groups remaining well within normal limits. 25-hydrox-vitamin D levels, on the other hand, showed modest increases after initiation of tirzepatide (mean 35.9 versus 44.5; d: 0.45; N = 70) or semaglutide (31.7 versus 37.4; d: 0.33; N = 46), which may be at least partially related to concomitant initiation of vitamin D supplementation at the time of incretin therapy initiation.

Brand-Specific Matched Analyses by Weight Loss and Baseline HbA1c

The different branded formulations of tirzepatide (e.g., Mounjaro, Zepbound) and semaglutide (e.g., Ozempic, Wegovy) have significant differences in approval timeline, initial indications, and real-world usage patterns. Specifically, Mounjaro and Ozempic were both initially approved for type 2 diabetes mellitus, while Zepbound and Wegovy were approved for chronic weight management. The brand distributions for all of the cohorts presented thus far are summarized in **Tables 11–13**. To assess whether the patterns observed at the compound level (tirzepatide versus semaglutide) were preserved within branded products, we performed additional 1:1 propensity-score matched comparisons of Zepbound versus Wegovy (N = 5,743 patients per arm) and Mounjaro versus Ozempic (N = 6,089 patients per arm), matched on age, race, sex, baseline BMI, and type 2 diabetes. Although it was not included as a matching variable, baseline HbA1c was well-balanced in each of the comparator cohort sets (**Figure 3B, Figure 3E**).

In the Zepbound-versus-Wegovy comparison, Zepbound was associated with a higher 12-month cumulative incidence of alopecia (5.3% vs. 3.6%; RR 1.47; P<0.001). This trend was directionally consistent, though not statistically significant, across all weight loss strata other than the ≤5% weight loss group (**Figure 3A**), which had similar rates of alopecia for Zepbound and Wegovy (2.4% versus 2.4%; RR 1.00; P>0.99). Similarly, incident alopecia was directionally higher with Zepbound in patients with baseline HbA1c less than 5.7% (4.9% versus 3.8%; RR 1.30; P=0.07) or between 5.7 to 6.5% band (4.5% versus 2.8%; RR 1.58; P=0.12) (**Figure 3C**).

In the Mounjaro-versus-Ozempic comparison, Mounjaro was associated with higher 12-month cumulative incidence of alopecia (3.7% vs. 2.6%; RR 1.44; P=0.001). These trends were directionally consistent in the ≤5% weight loss group (2.8% versus 1.8%; RR 1.56; P=0.04) and in the 5 to 10% weight loss group (3.0% versus 2.3%; RR 1.28; P=0.27) (**Figure 3D**). Across baseline HbA1c strata, incident alopecia was significantly higher after initiation of Mounjaro than Ozempic among patients with baseline HbA1c 5.7% to 6.5% (4.0% versus 2.2%; RR 1.83; P=0.02) and ≥6.5% (2.8% versus 1.3%; RR

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2.16; P=0.008), but no significant difference was seen in patients with baseline HbA1c less than 5.7% (3.4% versus 3.8%; RR 0.89; P=0.56) (**Figure 3F**).

GIPR-Enriched Dermato-Immune and Perivascular Receptor Expression in Alopecia-Relevant Skin Compartments

In an exploratory single-cell RNA-sequencing analysis of alopecia-relevant scalp and skin compartments, receptor prevalence was defined as the number of cells with detectable receptor expression divided by the total number of cells within each annotated tissue–cell population. Across the selected follicular, epithelial, dermato-immune, and perivascular populations, *GIPR* was detected more frequently than *GLP1R*, with *GLP1R* expression rare or absent in nearly all examined cell types (**Figure 12**).

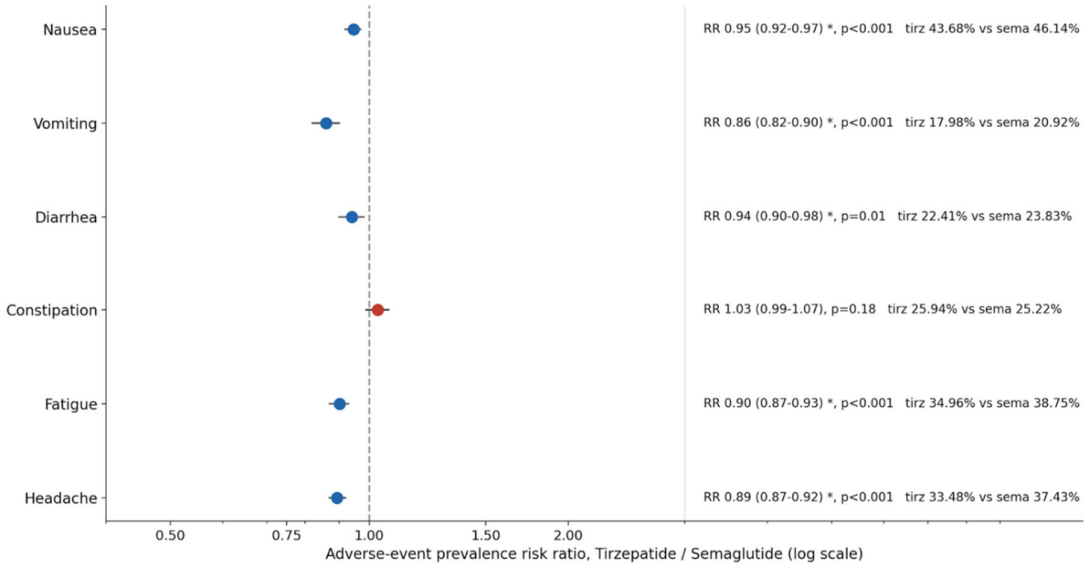

Figure 10. Positive-Control Adverse-Event Phenotypes in the Propensity-Score Matched Cohort. Shown are AI-curated clinical-note prevalence risk ratios for selected gastrointestinal and select systemic adverse events among tirzepatide and semaglutide users in the five-covariate propensity-score matched cohort. Points indicate risk ratios comparing tirzepatide with semaglutide, horizontal bars indicate 95% confidence intervals, and the dashed vertical line denotes no difference between treatment groups. Values below 1.0 indicate lower adverse-event prevalence after tirzepatide than after semaglutide. Blue points indicate adverse events less frequent after tirzepatide; red points indicate adverse events numerically higher after tirzepatide. Asterisks indicate statistically significant differences at P<0.05. The lower prevalence of nausea and vomiting after tirzepatide, consistent with prior federated EHR analyses, served as a positive-control benchmark confirming the AI-curated clinical-note pipeline detects known, directionally expected signals; see **Figure 11** for the true negative-control phenotype panel.

Scalp and body hair follicular keratinocytes (n = 5,441 cells) showed no detectable expression of either receptor. More general scalp and skin-of-body keratinocytes showed *GIPR* expression in 521 of 137,956 cells (0.38%), whereas *GLP1R* was detected in only 4 of 137,956 cells (0.003%). The strongest epithelial signal was observed in body-derived suprabasal keratinocytes, in which *GIPR* was detected in 172 of 1,824 cells (9.43%), while *GLP1R* was not detected in any cell. Melanocytes also showed higher *GIPR* prevalence, with expression in 256 of 12,084 cells (2.12%), compared with *GLP1R* expression in 2 of 12,084 cells (0.02%). Higher prevalence of *GIPR* than *GLP1R* was also observed across relevant dermato-immune populations, including natural killer cells (4.46% versus 0.03%; n = 18,536 cells), regulatory T cells (2.43% versus 0.01%; n = 33,689 cells),CD8-positive alpha-beta T cells (1.27% versus 0.01%; n = 48,594 cells), macrophages (0.97% versus 0.002%; n = 50,848 cells), dendritic cells (0.67% versus 0.002%; n = 43,448 cells), and mast cells (2.18% versus 0%; n = 4,366 cells). Skin-

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derived pericytes also showed evidence of higher *GIPR* expression compared to *GLP1R* (6.07% versus 0%; n = 17,895 cells).

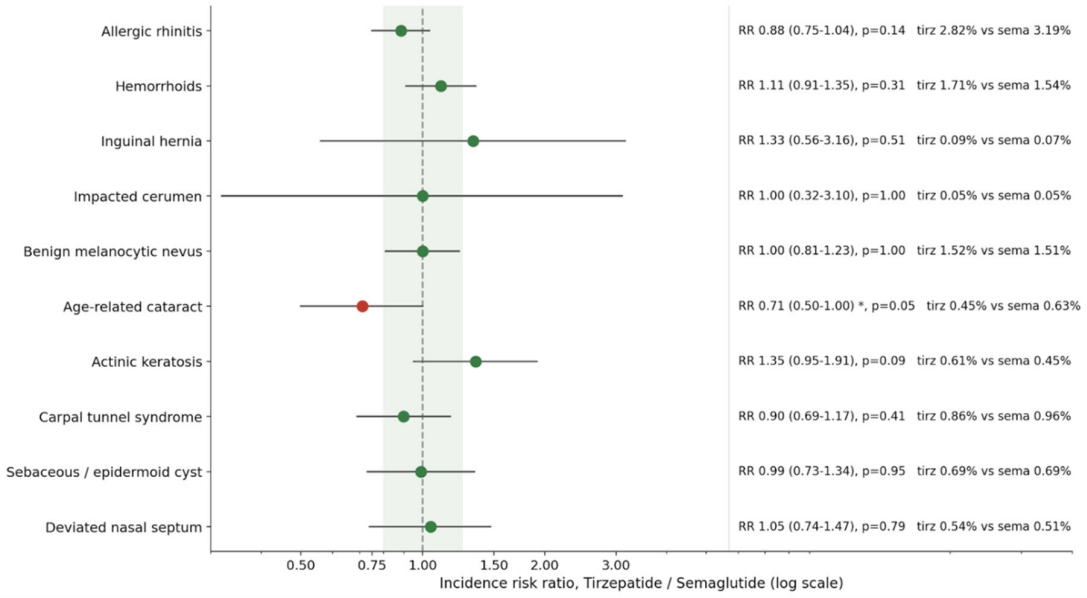

Figure 11. Negative-control outcomes in the PS-5 matched cohort, tirzepatide versus semaglutide. Shown are 12-month incidence risk ratios for ten phenotypes with no plausible relation to GLP-1 pharmacology, weight loss, or alopecia (baseline-negative, incident within the observation window). Points = risk ratio (tirzepatide/semaglutide); bars = 95% CI; the dashed line marks no difference and the shaded band marks 0.8-1.25. Risk ratios cluster around 1.0 with none reaching significance, supporting the absence of systematic between-cohort bias.

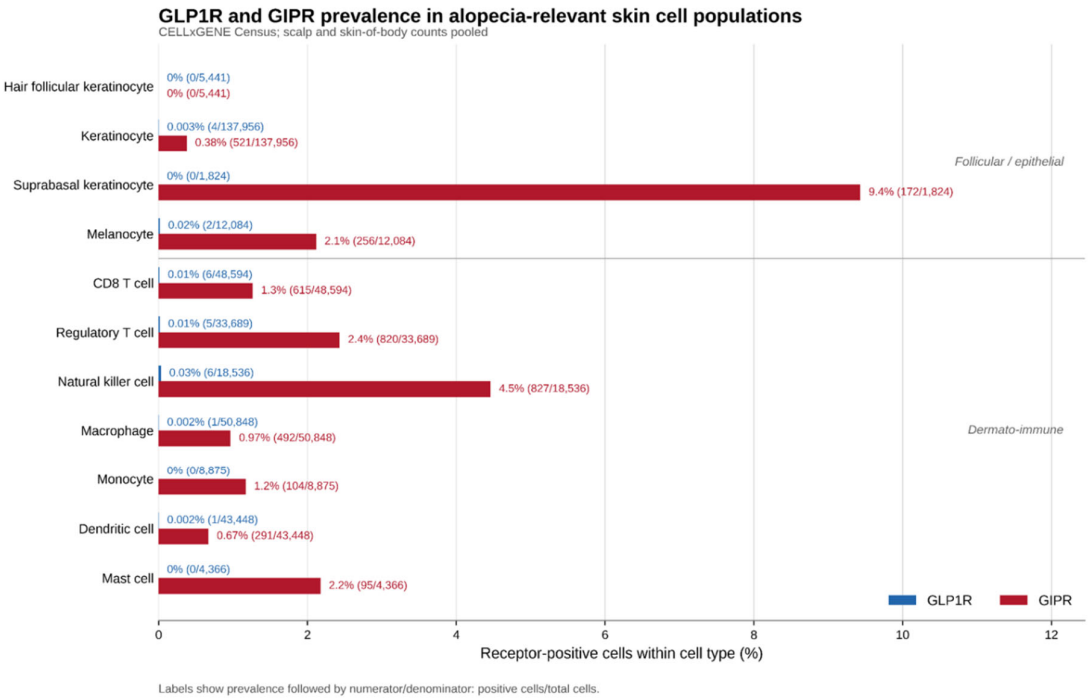

Figure 12. GIPR and GLP1R prevalence in alopecia-relevant dermato-immune cell populations. Single-cell RNA sequencing data from the CELLxGENE Census were analyzed to quantify receptor prevalence across

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alopecia-relevant skin cell populations. Bars show the percentage of cells within each annotated cell type with detectable GIPR (red) or GLP1R (blue) expression, calculated as the number of receptor-positive cells divided by the total number of cells in that tissue–cell type combination. Labels indicate the receptor prevalence followed by the numerator and denominator (receptor-positive cells/total cells). Hair follicular keratinocytes showed no detectable expression of either receptor, whereas GIPR was enriched in suprabasal keratinocytes and multiple dermato-immune cell populations, including natural killer cells, regulatory T cells, mast cells, CD8 T cells, monocytes, macrophages, and dendritic cells. In contrast, GLP1R expression was rare or absent across all examined cell types. .

While these data do not establish underlying mechanisms for the clinical observations, they are useful for hypothesis generation and raise the possibility that differential alopecia risk during dual GIP/GLP-1 receptor agonism may involve indirect effects on the follicular microenvironment, including immune, epithelial, or vascular pathways, with or without a component of direct effect on follicular keratinocytes.

Discussion

In this federated, head-to-head real-world study, new-onset alopecia was more frequent after tirzepatide initiation than after semaglutide initiation across multiple analytic views. The primary signal was not dependent on a single source of ascertainment: alopecia was detected predominantly through AI-curated clinical-note documentation, accrued progressively over the 12-month follow-up window, and was corroborated by greater post-index initiation of minoxidil. In the five-covariate propensity-score matched cohort, incident alopecia was higher after tirzepatide than after semaglutide, 4.20% versus 2.88%, with a risk ratio of 1.46. After additional matching on achieved weight-loss band, the association remained significant, 4.24% versus 3.33%, with a risk ratio of 1.27. Thus, achieved weight loss explained part, but not all, of the between-drug difference.

These results extend what is known from clinical trials and product labels. Tirzepatide and semaglutide both produce substantial weight loss, with tirzepatide producing mean body-weight reductions of 19.5% and 20.9% at the 10-mg and 15-mg doses in SURMOUNT-1, and semaglutide 2.4 mg producing a mean body-weight reduction of 14.9% in STEP 1 [1,2]. In current prescribing information, hair-loss adverse reactions are described as associated with weight reduction for both Zepbound and Wegovy. The Zepbound label reports hair loss more frequently among female than male patients, and the Wegovy label reports hair loss in 3.3% of adults treated with semaglutide 2.4 mg versus 1.0% with placebo, with higher rates among women than men [8,9]. Our study adds a real-world head-to-head comparison showing that the higher alopecia incidence after tirzepatide persisted even when achieved weight-loss band was directly balanced [1].

A weight-loss-associated component was nevertheless evident. Alopecia incidence increased with greater achieved weight loss within both treatment groups, and ICD-coded telogen effluvium was the subtype-specific signal of note. This is biologically plausible because telogen effluvium is a nonscarring diffuse shedding disorder that can follow metabolic stress, hormonal change, illness, medications, caloric restriction, sudden weight loss, or reduced protein intake [5–7]. The paired vitamin and mineral analyses did not show broad depletion of ferritin, vitamin B12, folate, vitamin D, or zinc among alopecia developers, although iron decreased slightly among tirzepatide-associated alopecia developers and should be evaluated in larger studies with paired iron indices and supplement data. These laboratory data argue against a simple global micronutrient depletion explanation, but they do not exclude nutritional mechanisms that were not measured, such as protein intake, caloric deficit, rapidity of weight loss, dietary quality, or transient deficiency not captured by available laboratory timing [7].

The persistence of the association after matching on achieved weight-loss band has potential mechanistic implications. Tirzepatide is a dual GIP and GLP-1 receptor agonist, whereas semaglutide primarily targets GLP-1R. Preclinical pharmacologic studies indicate that tirzepatide engages both receptors and exhibits signaling properties that differ from those of the native ligands [26,27]

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However, the present study does not establish that the observed difference in alopecia risk is receptor-mediated. The exploratory single-cell analysis did not identify detectable GIPR or GLP1R expression in canonical hair follicular keratinocytes, arguing against a dominant direct receptor-expression signal in these cells. Instead, GIPR expression was more prevalent than GLP1R across several alopecia-relevant dermato-immune and perivascular populations, including natural killer cells, regulatory T cells, CD8-positive T cells, macrophages, monocytes, dendritic cells, mast cells, and pericytes. GIPR was also detected in suprabasal keratinocytes and melanocytes, whereas GLP1R expression remained rare or absent across these populations. This distribution raises the possibility that any incretin-specific contribution to alopecia, if confirmed, may arise indirectly through changes in the follicular microenvironment rather than through direct agonism of canonical follicular keratinocytes. Potential pathways include immune-cell activity, perifollicular inflammation, vascular support, epithelial signaling, or interactions among skin, adipose, and stromal compartments. These observations are hypothesis-generating and should not be interpreted as evidence of a causal GIPR-mediated mechanism. Validation will require spatial transcriptomics, receptor protein localization, and functional perturbation studies in human scalp tissue. [26].

The sex-specific findings are clinically important. Female sex was the strongest baseline feature distinguishing alopecia developers from non-developers within both treatment arms. Among women, the tirzepatide-versus-semaglutide risk ratio was 1.50, and significant differences were observed across weight-loss, dose, and prescription-exposure strata. Developers in both arms also showed enrichment for prior alopecia or hair-loss history, thyroid disease, and autoimmune or reproductive-endocrine phenotypes, including hypothyroidism and, particularly among tirzepatide users, menstrual irregularity, ovarian dysfunction or hyperandrogenic endocrine disorder, and polycystic ovary syndrome. These patterns suggest that incident alopecia during incretin therapy may preferentially occur in patients with a baseline hormonal, autoimmune, or dermatologic predisposition rather than in patients with greater baseline cardiometabolic severity. This distinction matters because it supports more individualized counseling and surveillance rather than a generic message that weight loss itself inevitably causes hair loss.

Several internal-validity analyses strengthen interpretation. First, the cumulative-incidence curves separated gradually after the first several months rather than showing an immediate peri-index separation, arguing against a baseline coding artifact. Second, new starts of minoxidil were more frequent after tirzepatide than after semaglutide, providing a treatment-based corroboration of the clinical phenotype. Third, gastrointestinal and systemic note-derived adverse-event phenotypes served as a negative-control benchmark: nausea, vomiting, diarrhea, fatigue, and headache were lower after tirzepatide than after semaglutide, consistent with prior federated EHR observations, whereas alopecia was higher after tirzepatide. This supports the view that the alopecia signal was not simply a consequence of globally greater adverse-event documentation after tirzepatide.

The clinical implications are practical. Patients beginning tirzepatide or semaglutide, especially women and those with prior hair loss, thyroid disease, autoimmune features, or reproductive-endocrine phenotypes, should be counseled that diffuse shedding may occur during substantial weight loss and may resemble telogen effluvium. Such counseling should be balanced: clinically meaningful weight loss should not be equated with inevitable hair loss, and discontinuation should not be presumed necessary. Instead, clinicians should consider baseline and follow-up assessment of hair-loss history, menstrual or androgenic symptoms, thyroid status, iron indices, nutritional intake, protein adequacy, weight-loss velocity, and concomitant medications when clinically indicated. Early reassurance, avoidance of unnecessary discontinuation, and referral to dermatology for persistent, scarring, patchy, or diagnostically unclear hair loss may reduce patient distress while preserving cardiometabolic benefit.

These findings also have implications for pharmacovigilance. Hair-loss adverse events are undercaptured by structured ICD codes alone, as shown by the predominance of AI-curated clinical-note ascertainment. Conversely, note-based attribution is subject to awareness bias: public and clinical recognition of “Ozempic hair loss” may affect whether clinicians explicitly attribute hair loss

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to semaglutide or tirzepatide. Because public discourse and internet-search interest around GLP-1 weight loss have been especially anchored to Ozempic/semaglutide, and semaglutide-associated alopecia has already been explicitly discussed in dermatology literature [28–30], such awareness bias would be expected, if present, to increase hair-loss inquiry or attribution among semaglutide users rather than tirzepatide users. Accordingly, the observation of higher alopecia incidence after tirzepatide despite this potential bias argues that patient and clinician awareness of hair loss may need to be at least as strong for tirzepatide users, particularly because the Zepbound label reports hair loss as associated with weight reduction and more frequent among women [8,31]. The present study therefore supports a multi-signal approach to real-world safety evaluation that combines structured diagnoses, AI-curated clinical notes, assertion sentiment, event timing, medication new starts, matched comparators, and negative-control phenotypes. Such an approach may be particularly useful for adverse effects that are distressing to patients but inconsistently coded in routine care.

The study has limitations. It was observational, so residual confounding remains possible despite propensity-score matching and achieved-weight-loss-band matching. Weight-loss-band matching is a coarse adjustment and does not fully capture weight-loss velocity, nadir timing, caloric intake, protein sufficiency, lean-mass loss, dose escalation tempo, treatment interruption, or adherence. Alopecia was primarily ascertained from clinical notes, which may reflect patient reporting, clinician attention, and documentation behavior. Because women generally have higher outpatient and primary-care help-seeking than men, and because hair loss has substantial psychosocial impact among women, sex-related differences in symptom reporting, clinician inquiry, or documentation could have contributed to the female enrichment observed among alopecia developers [32–35]. This limitation may affect absolute incidence estimates and sex-stratified enrichment patterns, although it is less likely to fully explain the head-to-head tirzepatide-versus-semaglutide comparison because sex was balanced in the matched treatment arms. ICD-coded subtype events were sparse, so subtype-specific conclusions should be limited to telogen effluvium as a hypothesis-generating signal. Laboratory analyses were limited to patients with paired testing and did not capture dietary intake, supplement exposure, or all relevant nutrients. The receptor-expression analysis was external and exploratory; it does not demonstrate that GIPR signaling caused alopecia in treated patients. Finally, because this was a federated EHR study, results reflect patients who remained visible in participating health systems and may not generalize to all treated populations.

In conclusion, tirzepatide was associated with higher 12-month incident alopecia than semaglutide in matched real-world cohorts. The risk increased with achieved weight loss in both treatment groups, but the tirzepatide-associated excess persisted after matching on achieved weight-loss band, was enriched among women, included a telogen-effluvium subtype signal, accrued progressively over time, and was corroborated by greater initiation of hair-loss-directed therapy. Together, these findings support anticipatory counseling and targeted monitoring for alopecia during incretin-based weight-loss therapy, while motivating mechanistic studies of residual tirzepatide-associated risk, including fine-grained GLP1R-GIPR pharmacology and immune, vascular, endocrine, and nutritional pathways in human skin and scalp.

Supplementary Information: Table S1. Stratified incident alopecia (tirzepatide vs semaglutide, PS-5 matched): counts, rates, risk ratios, and P values. *Reference denominators for the stratified analyses summarized in the Results and shown in Figure 2 (A: maximum achieved weight-loss band; B: baseline HbA1c; C: change in HbA1c, defined as baseline minus the per-patient minimum achieved HbA1c). n/N = incident alopecia cases over patients at risk. RR = tirzepatide/semaglutide (Katz 95% CI); P from a two-proportion z-test. Provided so that the percentage-only values in the text have their denominators available, which is particularly relevant for smaller (potentially underpowered) strata.*

Data Availability Statement: This study involves the analysis of de-identified Electronic Health Record (EHR) data via the nference Federated System [36]. Data shown and reported in this manuscript were extracted from this environment using an established protocol for data extraction, aimed at preserving patient privacy. The data

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has been de-identified pursuant to an expert determination in accordance with the HIPAA Privacy Rule. Any data beyond what is reported in the manuscript, including but not limited to the raw EHR data, cannot be shared or released due to the parameters of the expert determination to maintain the data de-identification.

Code Availability: The analysis code is not publicly available. Please contact the corresponding author for details.

Conflicts of Interest: The authors are employees of nference, inc., which conducts research collaborations with various biopharmaceutical companies whose therapeutic products are included in this study. None of these companies, nor any other nference collaborator, funded, supported, or had any role in the independent study design, data acquisition, analysis, interpretation, manuscript preparation, or the decision to submit this work for publication. All analyses were conducted by the authors using de-identified electronic health record data. The authors declare no additional competing interests.

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