greater degree, suggesting the presence of other aggressive features in their tumors. Because little is known about the impact of KC, these findings suggest that health-related outcomes and quality-of-life measures may warrant further investigation.

Limitations include not capturing uninsured, publicly insured, or privately insured individuals who did not seek medical services. The true number of index KCs is likely underestimated due to our continuous enrollment restriction. Detailed demographic data, clinical information, or behavioral practices are also not available. Nevertheless, we report results and trends from a population for which there is a paucity of data.

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Proton pump inhibitors are associated with increased risk of alopecia areata: A nationwide nested case-control study

To the Editor: Alopecia areata (AA) is a common autoimmune disease.[1] Although the exact pathogenesis remains obscure, growing evidence has suggested a link between AA and the gastrointestinal microbiome, described as the skin-gut axis.[2] Moreno-Arrones et al[3] found bacterial biomarkers associated with the disease status of AA, which stressed the skin-gut axis. Meanwhile, prolonged use of proton pump inhibitors (PPIs) has been associated with gut dysbiosis.[4] This nationwide nested case-control study examined the association between PPI use and the risk of AA.

We identified all individuals exposed to any PPI between January 1998 and December 2013 from the National Health Insurance Research Database in Taiwan. The AA cases are defined as individuals without a history of hair and hair follicles diseases (International Classification of Diseases-Ninth Clinical Modification code 704) at the enrollment time and subsequently diagnosed with AA (code 704.01). The diagnosis of AA was made by board-certified dermatologists or rheumatologists. The time of the first PPI exposure and the time of AA diagnosis were defined as the enrollment time and the study end time, respectively.

For each AA patient, one control individual without AA was selected after matching for age, sex, residence, monthly premium, enrollment time, study end time, and comorbidity. The cumulative defined daily dose was used to quantify the PPI use. The standardized mean difference was used to compare baseline characteristics between study groups. Logistic regression analysis was used to evaluate the association between PPI use and AA risk.

We identified 35,552 patients with prior exposure to PPI (Table I). A dose-response relationship was found between PPI use and the risk of AA after

Table I. Demographic characteristics of patients who were exposed to proton pump inhibitors (*PPI*) with or without subsequent alopecia areata (*AA*)

Variable	Patients exposed to PPI		SMD*
	With subsequent AA (n = 17,776)	Without subsequent AA (n = 17,776)	
Age at enrollment/first time of PPI exposure, mean (SD), y	44.03 (15.98)	44.19 (15.93)	−0.1615
Sex, No. (%)			0.0000
Male	9931 (55.9)	9931 (55.9)	
Female	7845 (44.1)	7845 (44.1)	
Indications of PPI use, No. (%)			
Peptic ulcer	17,036 (95.8)	17,100 (96.2)	−0.0036
Gastrointestinal reflux disease	3229 (18.2)	2952 (16.6)	0.0156
Upper gastrointestinal bleeding	3658 (20.6)	3966 (22.3)	−0.0173
Comorbidities, No. (%)			
Hypertension	2751 (15.5)	2751 (15.5)	0.0000
Dyslipidemia	1490 (8.4)	1490 (8.4)	0.0000
Diabetes mellitus	1487 (8.4)	1487 (8.4)	0.0000
Obesity	44 (0.2)	44 (0.2)	0.0000
Autoimmune diseases	292 (1.6)	292 (1.6)	0.0000
Alcohol use disorders	380 (2.1)	380 (2.1)	0.0000
Neoplasms	3318 (18.7)	3318 (18.7)	0.0000
Thyroid diseases	294 (1.7)	294 (1.7)	0.0000
Atopic dermatitis	61 (0.3)	61 (0.3)	0.0000
Allergic rhinitis	2355 (13.2)	2355 (13.2)	0.0000
Allergic conjunctivitis	1300 (7.3)	1300 (7.3)	0.0000
Asthma	578 (3.3)	578 (3.3)	0.0000
Depressive disorders	434 (2.4)	434 (2.4)	0.0000
Psoriasis	14 (0.1)	14 (0.1)	0.0000
Charlson Comorbidity Index score at enrollment, mean (SD)	1.62 (1.32)	1.58 (1.31)	0.0409
Use of PPI during follow-up period			0.0718
cDDD, >365, No. (%)	1160 (6.5)	948 (5.3)	
cDDD, 121-365, No. (%)	4651 (26.2)	4309 (24.2)	
cDDD, 31-120, No. (%)	7561 (42.5)	7605 (42.8)	
cDDD, ≤30, No. (%)	4404 (24.8)	4914 (27.6)	
cDDD, mean (SD)	130.32 (202.95)	116.85 (185.91)	
Level of urbanization, No. (%)			0.0000
1 (most urbanized)	2344 (13.2)	2344 (13.2)	
2	4653 (26.2)	4653 (26.2)	
3	1287 (7.2)	1287 (7.2)	
4	1493 (8.4)	1493 (8.4)	
5 (most rural)	7999 (45.0)	7999 (45.0)	
Monthly premium, NTD			0.0000
≤15,840	6328 (35.6)	6328 (35.6)	
15,841−25,000	6164 (34.7)	6164 (34.7)	
≥25,001	5284 (29.7)	5284 (29.7)	
Follow-up duration, mean (SD), y	4.45 (3.42)	4.40 (3.44)	0.0476

cDDD, Cumulative defined daily dose; *NTD*, New Taiwan dollars; *SMD*, standardized mean difference.
*With subsequent AA vs without subsequent AA.

adjustment for potential confounders (Table II). These associations remained significant after being stratified by sex or PPI indications (Supplemental Table I, available via Mendeley at https://doi.org/10.17632/yfftz7j5xg.2). Among different types of PPIs, pantoprazole, lansoprazole, esomeprazole, and rabeprazole, but not omeprazole (odds ratio, 1.04; 95% confidence interval, 0.98-1.09), were associated with an increased risk of AA (Supplemental Table II).

Previous studies have found that inflammation in the gut may be a driver of AA.[2] The gut microbiota has been shown to play an important role in the systemic T-helper 17 cell/regulatory T-cell balance, which is relevant to the pathogenesis of AA.[5]

Table II. Logistical regression models of risk of alopecia areata among patients who were exposed to proton pump inhibitors (*PPIs*)

	Men	Women	All
Variable	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**
Use of PPIs during follow-up period			
cDDD, ≤30	1 [Reference]	1 [Reference]	1 [Reference]
cDDD, 31-120	**1.16 (1.08-1.24)**	1.07 (0.99-1.16)	**1.12 (1.06-1.18)**
cDDD, 121-365	**1.26 (1.16-1.36)**	**1.19 (1.09-1.29)**	**1.22 (1.15-1.29)**
cDDD, >365	**1.40 (1.24-1.59)**	**1.42 (1.22-1.66)**	**1.40 (1.27-1.54)**

cDDD, Cumulative defined daily dose; *CI*, confidence interval; *OR*, odds ratio.
*Adjusted for age, PPI indications, and Charlson Comorbidity Index score. Bold values are statistically significant.

Prolonged PPI use might lead to gut dysbiosis, thereafter causing T-helper 17/regulatory T-cell imbalance.[4] Overall, alteration of the gut flora after PPI use may explain the increased risk of AA in our study.

This study had several limitations. First, the impact of PPI use on the AA risk might be underestimated because only those who sought medical treatment were included in the study. Second, the National Health Insurance Research Database lacks information regarding disease severity, family history, and psychosocial stress. Third, we presumed that all medications were taken by the patients as prescribed, which could overestimate the actual ingested dosage. Finally, the potential confounding effects of PPI indications should be carefully assessed. To address this bias, we selected well-matched controls and adjusted for PPI indications in the analyses.

In conclusion, our study revealed PPI use is associated with an increased AA risk in a dose-dependent manner. Further studies are needed to elucidate the underlying mechanisms.

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