

Epithelial Barrier Diseases Among Adult Patients With Seborrheic Dermatitis

Sabrina Meng, BS; Ronald Berna, MD; Ole Hoffstad, MS; Junko Takeshita, MD, PhD, MSCE; Daniel Shin, PhD; Zelma C. Chiesa Fuxench, MD, MSCE; David J. Margolis, MD, PhD

 Supplemental content

IMPORTANCE The epithelial barrier theory (EBT) proposes that epithelial barrier disruption is implicated in the development of skin, respiratory, gastrointestinal, and ocular diseases (epithelial barrier diseases, or EBDs). There is a need to better understand the relationship between seborrheic dermatitis and EBDs, and we hypothesize that seborrheic dermatitis, characterized by epithelial barrier dysfunction, is associated with increased frequency of other EBDs.

OBJECTIVE To explore the association between seborrheic dermatitis and EBDs.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used a large US administrative claims database, which included data collected from multiple health care centers and patient care settings across the US from January 1, 2016, through June 30, 2022. This study consisted of patients aged 18 years and older at enrollment, with at least 1 year of continuous enrollment, and with a minimum of 2 visits on unique days to a medical professional. The mean (SD) patient follow-up time was 3.46 (1.80) years with a total follow-up of more than 70 million person-years. Individuals with missing data for demographic covariates, including age, sex, and division (ie, billing region), were excluded. Data were analyzed from January to September 2025.

EXPOSURES Diagnosis of seborrheic dermatitis at any point during the observation period.

MAIN OUTCOMES AND MEASURES Diagnosis of an EBD at any point during the observation period.

RESULTS Of 20 274 189 patients, 733 776 (3.62%) had seborrheic dermatitis (median [IQR] age, 62.63 [41.53-70.55] years; 54.7% female). Using adjusted models, seborrheic dermatitis was positively associated with atopic dermatitis (odds ratio [OR], 3.21; 95% CI, 3.18-3.24), alopecia areata (OR, 4.02; 95% CI, 3.93-4.11), contact dermatitis (OR, 2.25; 95% CI, 2.23-2.26), psoriasis (OR, 3.26; 95% CI, 3.23-3.29), rosacea (OR, 4.52; 95% CI, 4.49-4.56), hidradenitis suppurativa (OR, 1.63; 95% CI, 1.58-1.68), chronic spontaneous urticaria (OR, 1.35; 95% CI, 1.33-1.37), pemphigus vulgaris (OR, 1.48; 95% CI, 1.31-1.69), bullous pemphigoid (OR, 1.60; 95% CI, 1.51-1.70), rhinosinusitis (OR, 1.24; 95% CI, 1.24-1.25), celiac disease (OR, 1.36; 95% CI, 1.32-1.39), irritable bowel syndrome (OR, 1.32; 95% CI, 1.31-1.33), ocular allergy (OR, 1.39; 95% CI, 1.37-1.41), and dry eye (OR, 1.48; 95% CI, 1.48-1.49) and was negatively associated with chronic obstructive pulmonary disease (OR, 0.72; 95% CI, 0.71-0.72) and pulmonary hypertension (OR, 0.70; 95% CI, 0.69-0.71).

CONCLUSIONS AND RELEVANCE These findings support the EBT as a shared driver in the pathogenesis of seborrheic dermatitis and other diverse EBDs and encourage further investigation into the underlying mechanisms of disease pathogenesis.

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Author Affiliations: Perelman School of Medicine at the University of Pennsylvania, Philadelphia (Meng); Department of Dermatology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia (Berna, Hoffstad, Takeshita, Shin, Chiesa Fuxench, Margolis); Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia (Takeshita, Margolis).

Corresponding Author: Sabrina Meng, BS, Perelman School of Medicine at the University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104 (sabrina.meng@penmedicine.upenn.edu).

Seborrheic dermatitis is a common dermatologic condition that can present in infancy, adolescence, or adulthood.^{1,2} Seborrheic dermatitis commonly presents with erythema with overlying greasy scale localized primarily to the face, scalp, and other areas with high sebaceous gland activity.¹ Seborrheic dermatitis can be a chronic inflammatory skin condition and affects approximately 5% of the population worldwide.³ In addition to causing symptoms such as itching, flaking, and erythema, seborrheic dermatitis is associated with skin barrier dysfunction.³ Many factors are hypothesized to contribute to skin barrier disruption and inflammation in seborrheic dermatitis, including colonization by *Malassezia* yeast, release of lipases that result in keratinocyte lipid breakdown and changes in skin lipid matrix composition, and immunologic response and generation of cytokines against free fatty acids and lipid peroxides.⁴⁻⁸ Skin barrier disruption in seborrheic dermatitis has also been supported by evidence from electron microscopy studies, which show disorganized stratum corneum packing, as well as functional studies showing an increase in transepidermal water loss.^{9,10}

Epithelial barrier disruption has been implicated in the development of many epithelial barrier diseases (EBDs) of the skin, respiratory tract, gastrointestinal tract, and ocular surface.¹¹ The epithelial barrier theory (EBT) posits that these EBDs arise from epithelial barrier dysfunction, which results in host tissue exposure to pathogens, environmental pollutants, and allergens.^{11,12} These exposures lead to a cycle of pathological events that include pathogen and/or allergen migration to subepithelial areas, immune response, chronic inflammation, and impaired epithelial barrier healing.¹¹⁻¹⁴ The result of this damage is an inflammatory state, which is thought to contribute to the development of chronic inflammatory conditions.¹¹

Thus, we hypothesize that seborrheic dermatitis-associated epithelial barrier dysfunction may be associated with a chronic inflammatory state and an increased frequency of diseases specified by the EBT model, many of which are immunologically mediated.¹¹ Although some studies have reported associations between seborrheic dermatitis and a subset of EBDs, such as dermatologic conditions, the relationship between seborrheic dermatitis and other conditions thought to be mediated by EBDs remains unknown.¹⁵ In this study, we aim to evaluate the association between seborrheic dermatitis and other EBDs at any point during the observation period using a large administrative database.

Methods

This study was exempt from review by the University of Pennsylvania Institutional Review Board due to usage of deidentified data and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies. We conducted a retrospective cohort study using a population of 20 274 189 patients from Optum's deidentified Clinformatics Data Mart Database (Optum CDM). The cohort was limited to patients aged 18 years or older at enrollment, with at least 1 year of continuous enrollment

Key Points

Question Is seborrheic dermatitis associated with the development of other epithelial barrier diseases (EBDs)?

Findings In this cohort study of 20 274 189 patients, seborrheic dermatitis was positively associated with other EBDs, including atopic dermatitis, alopecia areata, contact dermatitis, psoriasis, rosacea, hidradenitis suppurativa, rhinosinusitis, celiac disease, irritable bowel syndrome, ocular allergy, and dry eye, but was negatively associated with chronic obstructive pulmonary disease and pulmonary hypertension.

Meaning These findings suggest that there are shared drivers in the pathogenesis of seborrheic dermatitis and EBDs that may be explained by the epithelial barrier theory and promote additional research into the mechanisms of disease pathogenesis.

between January 1, 2016, and June 30, 2022, representing the time frame of available data using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* coding. We required patients to have a minimum of 2 visits to medical professionals on separate days to minimize bias from health care nonutilization. We excluded individuals with missing data for any of the demographic covariates, including age, sex, and division (ie, billing region within the US). Additional details on cohort construction can be found in the eFigure in [Supplement 1](#).

Our selection of EBDs was derived from those published by Sun et al.¹¹ We focused on EBDs that primarily present at the epithelial surface (skin, respiratory, gastrointestinal, and ocular). Of these diseases, we excluded periodontitis and non-allergic rhinitis with eosinophilia syndrome due to concerns about diagnostic capture and accuracy, and food protein-induced enterocolitis because it primarily occurs in infants.¹⁶ The frequency of seborrheic dermatitis and EBDs was determined using *ICD-10* codes (eTable 1 in [Supplement 1](#)), which were verified against those in published literature when possible.¹⁷⁻⁴⁵ We defined a patient as having seborrheic dermatitis or an EBD if at least 1 *ICD-10* diagnosis code for the disease was logged for a claim during the patient's observation period. Because each of the EBDs was assumed to be positively associated with seborrheic dermatitis a priori, we introduced several conditions with no known association with seborrheic dermatitis to serve as negative controls (hand fracture, sebaceous cyst, appendicitis, influenza, and astigmatism).

Statistical Analysis

The primary outcome was the diagnosis of an EBD at any point during the observation period. Multivariable logistic regression was used to examine the association between seborrheic dermatitis and each EBD with an odds ratio (OR) and 95% CI. Patients without a seborrheic dermatitis diagnosis served as the comparison group. Given the large size of the cohort, we emphasized the clinical significance of the OR instead of considering only the magnitude of the *P* value. *P* values were 2-sided and reported as a verification of statistical significance with application of a Bonferroni correction. For this reason, any effect estimate, including its corresponding 95% CI,

Table 1. Characteristics for the Full Cohort, Patients With a Seborrheic Dermatitis Diagnosis, and Patients Without a Seborrheic Dermatitis Diagnosis

Characteristic	Full cohort (N = 20 274 189)	Diagnosis	
		Seborrheic dermatitis (n = 733 776)	No seborrheic dermatitis (n = 19 540 413)
Age at enrollment, median (IQR), y	53.54 (36.44-66.55)	62.63 (41.53-70.55)	53.21 (36.24-66.55)
Time in cohort, median (IQR), y	3.00 (2.00-5.00)	4.33 (2.58-6.50)	3.00 (2.00-4.89)
No. of visits, median (IQR)	23 (10-54)	53 (24-101)	23 (9-52)
Sex, No. (%)			
Female	11 023 540 (54.37)	379 699 (51.75)	10 643 841 (54.47)
Male	9 250 649 (45.63)	354 077 (48.25)	8 896 572 (45.53)
Division at time of enrollment, No. (%) ^a			
East North Central	2 927 805 (14.44)	87 155 (11.88)	2 840 650 (14.54)
East South Central	934 985 (4.61)	31 259 (4.26)	903 726 (4.62)
Middle Atlantic	1 594 637 (7.87)	63 372 (8.64)	1 531 265 (7.84)
Mountain	1 973 226 (9.73)	63 849 (8.70)	1 909 377 (9.77)
New England	789 126 (3.89)	28 881 (3.94)	760 245 (3.89)
Pacific	2 346 905 (11.58)	91 415 (12.46)	2 255 490 (11.54)
South Atlantic	4 740 928 (23.38)	216 489 (29.50)	4 524 439 (23.15)
West North Central	1 922 111 (9.48)	53 005 (7.22)	1 869 106 (9.57)
West South Central	3 044 466 (15.02)	98 351 (13.40)	2 946 115 (15.08)

^a Division at time of enrollment included East North Central: Illinois, Indiana, Michigan, Ohio, Wisconsin; East South Central: Alabama, Kentucky, Mississippi, Tennessee; Middle Atlantic: New Jersey, New York, Pennsylvania; Middle Atlantic: New Jersey, New York, Pennsylvania; Mountain: Arizona, Colorado, Indiana, Montana, Nevada, New Mexico, Utah, Wyoming; New England: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont; Pacific: Alaska, California, Hawaii, Oregon, Washington; South Atlantic: Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia; West North Central: Iowa, Kansas, Montana, Missouri, Nebraska, North Dakota, South Dakota; West South Central: Arkansas, Louisiana, Oklahoma, Texas.

that was not greater than 1.19 or less than 0.84 was not considered to be clinically significant a priori. Additionally, we calculated E-values as a measure of result robustness.^{46,47} E-values represent the minimum effect size that an unmeasured confounder needs to have with both the exposure and outcome to explain away an association.⁴⁷

Multivariable analysis included sex, age at enrollment, division at enrollment, time in cohort, and number of visits on unique days to a clinician (log-transformed for right-skewed distribution). Sensitivity analyses included adjustment for a concurrent diagnosis of atopic dermatitis (AD) or psoriasis and the exclusion of individuals with AD or psoriasis, which were performed because of the potential for misdiagnosis of seborrheic dermatitis as AD and psoriasis.⁴⁸ In addition, we performed analyses omitting each of the following covariates: age, sex, division, time in cohort, and number of visits on unique days (log-transformed). We performed an analysis in which diagnosis of seborrheic dermatitis required a seborrheic dermatitis code to be logged at 2 separate encounters to evaluate the impact of a stronger primary end point (ie, seborrheic dermatitis diagnosis) on the observed associations. Finally, to explore the potential for diagnostic bias in dermatologic conditions, a subcohort of individuals who had at least 1 dermatologist visit was evaluated.

All analyses were conducted using Stata MP, version 18 (StataCorp LLC). Data analyses were conducted from January to September 2025.

Results

In the cohort of 20 274 189 individuals, 733 776 individuals (3.62%) had at least 1 diagnosis of seborrheic dermatitis during their observation period. The mean (SD) patient follow-up time was 3.46 (1.80) years with a total follow-up of more than

70 million person-years. The median (IQR) age at enrollment was 62.63 (41.53-70.55) years among those with a seborrheic dermatitis diagnosis, vs 53.21 (36.24-66.55) years among those without seborrheic dermatitis. Patients diagnosed with seborrheic dermatitis were more likely to be male (48.25%, vs 51.75% female) when compared with the full cohort (45.53%, vs 54.47% female) and from the Middle Atlantic, Pacific, and South Atlantic regions of the US. The characteristics of the cohort are summarized in **Table 1**. Characteristics of additional subcohorts used in sensitivity analyses can be found in eTables 2-4 in **Supplement 1**.

The findings from the primary analysis, along with select secondary analyses, are shown in **Table 2**. Age-stratified and overall EBD frequencies, both raw and age-adjusted, for individuals with seborrheic dermatitis and without seborrheic dermatitis are presented in **Table 3** and **Table 4**, respectively. All dermatologic conditions were positively associated with seborrheic dermatitis, including AD (OR, 3.21; 95% CI, 3.18-3.24), alopecia areata (OR, 4.02; 95% CI, 3.93-4.11), contact dermatitis (OR, 2.25; 95% CI, 2.23-2.26), psoriasis (OR, 3.26; 95% CI, 3.23-3.29), rosacea (OR, 4.52; 95% CI, 4.49-4.56), hidradenitis suppurativa (OR, 1.63; 95% CI, 1.58-1.68), chronic spontaneous urticaria (CSU) (OR, 1.35; 95% CI, 1.33-1.37), pemphigus vulgaris (OR, 1.48; 95% CI, 1.31-1.69), and bullous pemphigoid (OR, 1.60; 95% CI, 1.51-1.70). Other EBDs positively associated with seborrheic dermatitis included rhinosinusitis (OR, 1.24; 95% CI, 1.24-1.25), celiac disease (OR, 1.36; 95% CI, 1.32-1.39), irritable bowel syndrome (OR, 1.32; 95% CI, 1.31-1.33), ocular allergy (OR, 1.39; 95% CI, 1.37-1.41), and dry eye (OR, 1.48; 95% CI, 1.48-1.49). Two EBDs were negatively associated with seborrheic dermatitis, namely chronic obstructive pulmonary disease (COPD) (OR, 0.72; 95% CI, 0.71-0.72) and pulmonary hypertension (OR, 0.70; 95% CI, 0.69-0.71). E-values for clinically significant associations ranged from 1.47 to 8.51.

Table 2. Analysis of the Association Between Seborrheic Dermatitis and Other Epithelial Barrier Diseases

Disease	OR (95% CI) ^a			Fully adjusted, OR E-value (CI E-value)
	Unadjusted	Adjusted		
		Partially ^c	Fully ^d	
Skin				
Atopic dermatitis	4.53 (4.50-4.57) ^e	3.83 (3.80-3.87) ^e	3.21 (3.18-3.24) ^e	5.87 (5.81)
Alopecia areata	5.04 (4.94-5.15) ^e	4.72 (4.62-4.82) ^e	4.02 (3.93-4.11) ^e	7.50 (7.32)
Contact dermatitis	3.19 (3.17-3.21) ^e	2.64 (2.62-2.66) ^e	2.25 (2.23-2.26) ^e	3.93 (3.89)
Psoriasis	4.43 (4.40-4.47) ^e	3.84 (3.80-3.87) ^e	3.26 (3.23-3.29) ^e	5.97 (5.91)
Rosacea	6.02 (5.98-6.06) ^e	5.24 (5.20-5.28) ^e	4.52 (4.49-4.56) ^e	8.51 (8.45)
Hidradenitis suppurativa	1.98 (1.92-2.04) ^e	2.07 (2.01-2.13) ^e	1.63 (1.58-1.68) ^e	2.64 (2.54)
Chronic spontaneous urticaria	1.92 (1.90-1.94) ^e	1.66 (1.64-1.68) ^e	1.35 (1.33-1.37) ^e	2.04 (1.99)
Pemphigus vulgaris	2.55 (2.25-2.89) ^e	1.93 (1.70-2.19) ^e	1.48 (1.31-1.69) ^e	2.32 (1.95)
Bullous pemphigoid	3.17 (3.00-3.36) ^e	2.12 (2.00-2.24) ^e	1.60 (1.51-1.70) ^e	2.58 (2.39)
Respiratory				
Asthma	1.37 (1.36-1.38) ^e	1.25 (1.24-1.25) ^e	0.97 (0.96-0.98) ^e	1.21 (1.16)
Rhinosinusitis	1.86 (1.85-1.87) ^e	1.57 (1.56-1.58) ^e	1.24 (1.24-1.25) ^e	1.47 (1.47)
Chronic obstructive pulmonary disease	1.38 (1.37-1.39) ^e	0.96 (0.96-0.97) ^e	0.72 (0.71-0.72) ^e	2.12 (2.12)
Sarcoidosis	1.55 (1.49-1.61) ^e	1.28 (1.24-1.33) ^e	0.97 (0.94-1.01) ^f	1.21 (1.00)
Pulmonary hypertension	1.52 (1.50-1.53) ^e	1.01 (0.99-1.02) ^f	0.70 (0.69-0.71) ^e	2.21 (2.17)
Idiopathic pulmonary fibrosis	1.81 (1.78-1.83) ^e	1.22 (1.20-1.24) ^e	0.90 (0.89-0.92) ^e	1.46 (1.39)
Cystic fibrosis	1.54 (1.38-1.71) ^e	1.45 (1.30-1.62) ^e	0.98 (0.88-1.09) ^f	1.16 (1.00)
Gastrointestinal				
Eosinophilic esophagitis	1.57 (1.52-1.63) ^e	1.47 (1.42-1.53) ^e	1.15 (1.10-1.19) ^e	1.57 (1.43)
Gastroesophageal reflux disease	1.77 (1.77-1.78) ^e	1.38 (1.38-1.39) ^e	1.01 (1.01-1.02) ^g	1.08 (1.08)
Barrett esophagus	1.99 (1.96-2.02) ^e	1.45 (1.42-1.47) ^e	1.13 (1.11-1.15) ^e	1.51 (1.46)
Food allergy	1.86 (1.84-1.89) ^e	1.64 (1.62-1.66) ^e	1.21 (1.19-1.22) ^e	1.71 (1.67)
Inflammatory bowel disease	1.66 (1.64-1.69) ^e	1.41 (1.38-1.43) ^e	1.08 (1.06-1.10) ^e	1.37 (1.31)
Celiac disease	1.94 (1.89-1.99) ^e	1.78 (1.73-1.83) ^e	1.36 (1.32-1.39) ^e	2.06 (1.97)
Diverticulosis	1.90 (1.89-1.91) ^e	1.31 (1.30-1.31) ^e	1.04 (1.03-1.05) ^e	1.24 (1.21)
Microscopic colitis	1.58 (1.56-1.59) ^e	1.29 (1.28-1.30) ^e	0.98 (0.97-0.99) ^e	1.16 (1.11)
Irritable bowel syndrome	2.01 (1.99-2.03) ^e	1.74 (1.73-1.76) ^e	1.32 (1.31-1.33) ^e	1.97 (1.95)
Ocular				
Ocular allergy	2.08 (2.05-2.11) ^e	1.70 (1.68-1.73) ^e	1.39 (1.37-1.41) ^e	2.13 (2.08)
Macular degeneration	2.06 (2.05-2.08) ^e	1.36 (1.35-1.37) ^e	1.16 (1.15-1.17) ^e	1.59 (1.57)
Dry eye	2.40 (2.39-2.41) ^e	1.81 (1.80-1.82) ^e	1.48 (1.48-1.49) ^e	2.32 (2.32)
Glaucoma	1.70 (1.69-1.71) ^e	1.21 (1.20-1.22) ^e	1.03 (1.02-1.04) ^e	1.21 (1.16)
Uveitis	1.63 (1.60-1.66) ^e	1.24 (1.21-1.26) ^e	0.98 (0.96-1.00) ^f	1.16 (1.00)
Other				
Hand fracture	1.36 (1.34-1.38) ^e	1.09 (1.08-1.11) ^e	0.90 (0.88-0.91) ^e	1.46 (1.43)
Sebaceous cyst	2.34 (2.32-2.37) ^e	1.82 (1.80-1.84) ^e	1.55 (1.53-1.56) ^e	2.47 (2.43)
Appendicitis	1.22 (1.18-1.25) ^e	1.10 (1.07-1.14) ^e	0.93 (0.90-0.96) ^e	1.36 (1.25)
Influenza	1.32 (1.31-1.34) ^e	1.16 (1.15-1.17) ^e	0.98 (0.97-0.99) ^f	1.16 (1.11)
Astigmatism	1.67 (1.66-1.68) ^e	1.23 (1.22-1.24) ^e	1.08 (1.08-1.09) ^e	1.37 (1.37)

Abbreviation: OR, odds ratio.

^a All *P* values were adjusted using Bonferroni correction for 35 hypotheses.^b The lower bound of the confidence interval is reported, as is common for E-values.^c Adjusted for age, sex, division, and time in cohort. Number of visits was not included in the model.^d Adjusted for age, sex, division, time in cohort, and number of visits.^e *P* < .001.^f *P* > .99.^g *P* = .002.

When analyzing conditions that served as negative controls, seborrheic dermatitis was less likely to be associated with hand fracture (OR, 0.90; 95% CI, 0.88-0.91), appendicitis (OR, 0.93; 95% CI, 0.90-0.96), and influenza (OR, 0.98; 95% CI, 0.97-0.99), but more likely to be associated with astigmatism (OR, 1.08; 95% CI, 1.08-1.09) and sebaceous cyst (OR, 1.55; 95% CI,

1.53-1.56). However, in a secondary analysis limited to individuals seen by a dermatologist, which was completed to evaluate the potential for diagnostic bias in dermatologic conditions, the association between seborrheic dermatitis and sebaceous cyst was minimal (OR, 1.10; 95% CI, 1.08-1.11), indicating clinically insignificant associations between sebor-

Table 3. Age-Stratified, Overall, and Age-Adjusted Epithelial Barrier Disease Frequencies Among Patients With Seborrheic Dermatitis

Disease	Age group, No. (%), y ^a				Overall, No. (%) (n = 733 776)	Overall, age-adjusted % ^b
	<36 (n = 135 980)	36-54 (n = 152 438)	54-67 (n = 191 929)	≥67 (n = 253 429)		
Skin						
Atopic dermatitis	14 345 (10.55)	15 814 (10.37)	18 885 (9.84)	25 747 (10.16)	74 791 (10.19)	10.24
Alopecia areata	3482 (2.56)	2878 (1.89)	2021 (1.05)	1818 (0.72)	10 199 (1.39)	1.69
Contact dermatitis	16 297 (11.98)	22 670 (14.87)	29 349 (15.29)	40 367 (15.93)	108 683 (14.81)	14.14
Psoriasis	10 444 (7.68)	14 707 (9.65)	18 813 (9.80)	21 776 (8.59)	65 740 (8.96)	8.82
Rosacea	15 557 (11.44)	24 641 (16.16)	28 202 (14.69)	30 922 (12.20)	99 322 (13.54)	13.48
Hidradenitis suppurativa	1879 (1.38)	1454 (0.95)	788 (0.41)	479 (0.19)	4600 (0.63)	0.84
Chronic spontaneous urticaria	5475 (4.03)	6209 (4.07)	7145 (3.72)	8668 (3.42)	27 497 (3.75)	3.82
Pemphigus vulgaris	27 (0.02)	45 (0.03)	71 (0.04)	124 (0.05)	267 (0.04)	0.03
Bullous pemphigoid	20 (0.01)	63 (0.04)	292 (0.15)	938 (0.37)	1313 (0.18)	0.13
Respiratory						
Asthma	15 358 (11.29)	21 062 (13.82)	29 784 (15.52)	36 752 (14.50)	102 956 (14.03)	13.5
Rhinosinusitis	39 886 (29.33)	53 487 (35.09)	69 984 (36.46)	93 045 (36.71)	256 402 (34.94)	33.61
Chronic obstructive pulmonary disease	635 (0.47)	5748 (3.77)	28 457 (14.83)	57 271 (22.60)	92 111 (12.55)	8.69
Sarcoidosis	157 (0.12)	671 (0.44%)	1123 (0.59)	1071 (0.42)	3022 (0.41)	0.37
Pulmonary hypertension	302 (0.22)	1653 (1.08)	7952 (4.14)	24 302 (9.59)	34 209 (4.66)	3.14
Idiopathic pulmonary fibrosis	251 (0.18)	1369 (0.90)	5998 (3.13)	14 345 (5.66)	21 963 (2.99%)	2.02
Cystic fibrosis	100 (0.07)	61 (0.04)	69 (0.04)	116 (0.05)	346 (0.05%)	0.05
Gastrointestinal						
Eosinophilic esophagitis	659 (0.48)	1003 (0.66)	738 (0.38)	556 (0.22)	2956 (0.40%)	0.46
Gastroesophageal reflux disease	21 006 (15.45)	43 197 (28.34)	81 153 (42.28)	123 618 (48.78)	268 974 (36.66)	30.95
Barrett esophagus	426 (0.31)	2335 (1.53)	6701 (3.49)	9614 (3.79)	19 076 (2.60)	1.94
Food allergy	6066 (4.46)	5764 (3.78)	5536 (2.88)	6942 (2.74)	24 308 (3.31)	3.59
Inflammatory bowel disease	2355 (1.73)	3488 (2.29)	5221 (2.72)	6807 (2.69)	17 871 (2.44)	2.26
Celiac disease	1162 (0.85)	1356 (0.89)	1343 (0.70)	1605 (0.63)	5466 (0.74)	0.78
Diverticulosis	2378 (1.75)	21 328 (13.99)	60 189 (31.36)	87 138 (34.38)	171 033 (23.31)	17.18
Microscopic colitis	8103 (5.96)	10 096 (6.62)	16 050 (8.36)	24 877 (9.82)	59 126 (8.06)	7.33
Irritable bowel syndrome	7033 (5.17)	9799 (6.43)	13 997 (7.29)	19 295 (7.61)	50 124 (6.83)	6.41
Ocular						
Ocular allergy	3493 (2.57)	4875 (3.20)	6683 (3.48)	8753 (3.45)	23 804 (3.24)	3.07
Macular degeneration	317 (0.23)	2369 (1.55)	17 157 (8.94)	59 929 (23.65)	79 772 (10.87)	6.96
Dry eye	10 978 (8.07)	23 580 (15.47)	56 774 (29.58)	103 337 (40.78)	194 669 (26.53)	20.52
Glaucoma	3926 (2.89)	12 405 (8.14)	37 163 (19.36)	68 511 (27.03)	122 005 (16.63)	12.21
Uveitis	929 (0.68)	1839 (1.21)	3263 (1.70)	5020 (1.98)	11 051 (1.51)	1.27
Other						
Hand fracture	1726 (1.27)	2637 (1.73)	4489 (2.34)	7043 (2.78)	15 895 (2.17)	1.90
Sebaceous cyst	4839 (3.56)	6588 (4.32)	9628 (5.02)	13 515 (5.33)	34 570 (4.71)	4.34
Appendicitis	918 (0.68)	1006 (0.66)	1072 (0.56)	1167 (0.46)	4163 (0.57)	0.60
Influenza	10 958 (8.06)	11 645 (7.64)	10 273 (5.35)	12 679 (5.00)	45 555 (6.21)	6.79
Astigmatism	4405 (3.24)	9640 (6.32)	31 276 (16.30)	46 332 (18.28)	91 653 (12.49)	9.24

^a Age is stratified by quartiles derived from the statistics of the full cohort. The lower age bound is inclusive, and the upper age bound is exclusive.

^b Age-adjusted frequencies were calculated based on population estimates from 2022 US Census data using 5-year age brackets.

rheic dermatitis and negative controls. In the same secondary analysis, we found persistent positive associations between seborrheic dermatitis and AD (OR, 1.82; 95% CI, 1.80-1.83), alopecia areata (OR, 2.05; 95% CI, 2.00-2.10), contact dermatitis (OR, 1.47; 95% CI, 1.46-1.48), psoriasis (OR, 1.89; 95% CI, 1.87-1.91), rosacea (OR, 2.20; 95% CI, 2.19-2.22), and CSU

(OR, 1.82; 95% CI, 1.80-1.83) (eTable 8 in [Supplement 1](#)). All estimates were fully adjusted for age, sex, division, time in cohort, and number of visits. After adjustment, number of visits had the greatest impact on effect estimates (Table 2). Results for all sensitivity analyses can be found in eTables 5-8 in [Supplement 1](#).

Table 4. Age-Stratified, Overall, and Age-Adjusted Epithelial Barrier Disease Frequencies Among Patients Without Seborrheic Dermatitis

	Age group, No. (%), y ^a					
Disease	<36 (n = 4 827 033)	36-54 (n = 5 187 822)	54-67 (n = 4 931 962)	≥67 (n = 4 593 594)	Overall, No. (%), (n = 19 540 413)	Overall, age-adjusted % ^b
Skin						
Atopic dermatitis	108 212 (2.24)	117 009 (2.26)	121 392 (2.46)	130 601 (2.84)	477 214 (2.44)	2.38
Alopecia areata	18 078 (0.37)	17 562 (0.34)	11 205 (0.23)	7619 (0.17)	54 464 (0.28)	0.29
Contact dermatitis	204 263 (4.23)	268 781 (5.18)	266 649 (5.41)	269 381 (5.86)	1 009 074 (5.16)	5.02
Psoriasis	62 566 (1.30)	114 472 (2.21)	134 254 (2.72)	113 001 (2.46)	424 293 (2.17)	2.07
Rosacea	81 306 (1.68)	146 850 (2.83)	144 647 (2.93)	122 409 (2.66)	495 212 (2.53)	2.43
Hidradenitis suppurativa	25 354 (0.53)	21 218 (0.41)	10 996 (0.22)	4443 (0.10)	62 011 (0.32)	0.35
Chronic spontaneous urticaria	96 365 (2.00)	105 907 (2.04)	96 764 (1.96)	89 190 (1.94)	388 226 (1.99)	1.97
Pemphigus vulgaris	169 (<0.01)	505 (0.01)	840 (0.02)	1274 (0.03)	2788 (0.01)	0.01
Bullous pemphigoid	153 (<0.01)	590 (0.01)	2467 (0.05)	7824 (0.17)	11 034 (0.06)	0.05
Respiratory						
Asthma	414 710 (8.59)	533 856 (10.29)	588 650 (11.94)	541 261 (11.78)	2 078 477 (10.64)	10.37
Rhinosinusitis	871 820 (18.06)	1 174 219 (22.63)	1 193 367 (24.20)	1 135 484 (24.72)	4 374 890 (22.39)	21.78
Chronic obstructive pulmonary disease	16 483 (0.34)	182 220 (3.51)	672 680 (13.64)	974 471 (21.21)	1 845 854 (9.45)	8.10
Sarcoidosis	2696 (0.06)	13 575 (0.26)	20 387 (0.41)	15 424 (0.34)	52 082 (0.27)	0.24
Pulmonary hypertension	6737 (0.14)	41 133 (0.79)	164 604 (3.34)	397 463 (8.65)	609 937 (3.12)	2.68
Idiopathic pulmonary fibrosis	5497 (0.11)	29 761 (0.57)	103 733 (2.10)	188 925 (4.11)	327 916 (1.68)	1.42
Cystic fibrosis	2285 (0.05)	1263 (0.02)	1153 (0.02)	1288 (0.03)	5989 (0.03)	0.03
Gastrointestinal						
Eosinophilic esophagitis	14 154 (0.29)	18 275 (0.35)	11 024 (0.22)	6619 (0.14)	50 072 (0.26)	0.27
Gastroesophageal reflux disease	463 297 (9.60)	1 019 252 (19.65)	1 541 887 (31.26)	1 781 980 (38.79)	4 806 416 (24.60)	22.60
Barrett esophagus	8508 (0.18)	45 635 (0.88)	100 358 (2.03)	103 741 (2.26)	258 242 (1.32)	1.14
Food allergy	96 814 (2.01)	96 422 (1.86)	80 266 (1.63)	79 532 (1.73)	353 034 (1.81)	1.82
Inflammatory bowel disease	43 818 (0.91)	71 824 (1.38)	87 205 (1.77)	86 439 (1.88)	289 286 (1.48)	1.40
Celiac disease	18 429 (0.38)	21 917 (0.42)	18 640 (0.38)	16 321 (0.36)	75 307 (0.39)	0.39
Diverticulosis	51 543 (1.07)	462 945 (8.92)	1 042 282 (21.13)	1 134 704 (24.70)	2 691 474 (13.77)	11.78
Microscopic colitis	194 345 (4.03)	227 382 (4.38)	278 407 (5.64)	328 330 (7.15)	1 028 464 (5.2)	5.04
Irritable bowel syndrome	119 192 (2.47)	169 868 (3.27)	195 172 (3.96)	202 393 (4.41)	686 625 (3.51)	3.37
Ocular						
Ocular allergy	57 619 (1.19)	78 936 (1.52)	85 614 (1.7)	88 135 (1.92)	310 304 (1.59)	1.52
Macular degeneration	5237 (0.11)	42 516 (0.82)	259 019 (5.25)	785 155 (17.09)	1 091 927 (5.59)	4.74
Dry eye	156 676 (3.25)	373 729 (7.20)	815 437 (16.53)	1 209 457 (26.33)	2 555 299 (13.08)	11.37
Glaucoma	71 783 (1.49)	260 566 (5.02)	684 173 (13.87)	1 030 981 (22.44)	2 047 503 (10.48)	8.97
Uveitis	20 876 (0.43)	37 054 (0.71)	56 499 (1.15)	67 335 (1.47)	181 764 (0.93)	0.85
Other						
Hand fracture	61 684 (1.28)	68 859 (1.33)	81 711 (1.66)	100 743 (2.19)	312 997 (1.60)	1.55
Sebaceous cyst	68 420 (1.42)	102 922 (1.98)	116 236 (2.36)	116 385 (2.53)	403 963 (2.07)	1.96
Appendicitis	29 221 (0.61)	26 698 (0.51)	20 125 (0.41)	15 282 (0.33)	91 326 (0.47)	0.48
Influenza	286 305 (5.93)	284 239 (5.48)	188 581 (3.82)	171 543 (3.73)	930 668 (4.76)	4.94
Astigmatism	112 695 (2.33)	220 926 (4.26)	564 803 (11.45)	641 415 (13.96)	1 539 839 (7.88)	6.72

^a Age is stratified by quartiles derived from the statistics of the full cohort. The lower age bound is inclusive, and the upper age bound is exclusive.

^b Age-adjusted frequencies were calculated based on population estimates from 2022 US Census data using 5-year age brackets.

Discussion

In this retrospective cohort study, several dermatologic EBDs were associated with seborrheic dermatitis, including atopic dermatitis, alopecia areata, contact dermatitis, psoriasis, rosacea, hidradenitis suppurativa, chronic spontaneous urti-

caria, pemphigus vulgaris, and bullous pemphigoid. Although possible misdiagnosis of seborrheic dermatitis as AD or psoriasis could contribute to these associations, sensitivity analyses adjusting for a concurrent diagnosis of AD or psoriasis or excluding patients with a diagnosis of AD or psoriasis yielded similar results, indicating that misdiagnosis does not significantly impact effect estimates (eTable 5 in [Supple-](#)

ment 1). Furthermore, the E-value analysis indicated that an unmeasured confounder would need to have a OR greater than 5.81 for AD and 5.91 for psoriasis to negate the association with seborrheic dermatitis. This effect estimate is greater than any of the associations that we report and is unlikely to exist. The positive association between seborrheic dermatitis and dermatologic conditions is consistent with the literature, although it should be noted that findings on the association between seborrheic dermatitis and AD have been variable, with some studies reporting a negative association and others reporting a positive association, especially for seborrheic dermatitis diagnosed in infancy.^{15,49} The etiology of the dermatologic conditions examined in this study have been found to involve diverse inflammatory markers and mechanisms, spanning both Th1 and Th2 pathways.¹¹ Thus, the positive associations between seborrheic dermatitis and these dermatologic conditions lends support to the EBT model, suggesting that epithelial dysfunction from seborrheic dermatitis leads to a generalized increase in inflammatory skin disorders irrespective of the specific immunological pathway.

Additionally, we found positive associations between seborrheic dermatitis and diseases of other epithelial barriers, including rhinosinusitis, celiac disease, irritable bowel syndrome, ocular allergy, and dry eye. Although the associations between seborrheic dermatitis and these EBDs have not all been reported on extensively in the literature, our results corroborate the positive association previously found between seborrheic dermatitis and dry eye.^{11,50} These findings further support the role of the EBT model in the pathogenesis of EBDs and that disruption at 1 epithelial barrier (eg, skin) can increase the frequency of inflammatory conditions at not only that barrier, but also at other types of epithelial barriers (eg, respiratory, gastrointestinal, and ocular). This observation may be explained by a sequence of epithelial disruption, immune sensitization to antigens, systemic inflammation, and exposure to shared antigens at different epithelial surfaces, linking the pathogenesis of seborrheic dermatitis and a diverse set of EBDs.

Some EBDs were negatively associated with seborrheic dermatitis, including COPD and pulmonary hypertension. We believe that the negative associations between seborrheic dermatitis and COPD and pulmonary hypertension may be explained by differences in structure, physiology, and immunological mechanisms at different epithelial barriers.¹¹ For example, EBT-mediated pathogenesis may be partially explained by damaged epithelial cells releasing inflammatory cytokines such as interleukin (IL)-1, IL-25, and IL-33, which leads to the influx and activation of immune cells.^{51,52} However, these cytokines have varying significance at different locations, with IL-25 being more prominent in gastrointestinal disorders, IL-33 in lung and gastrointestinal disorders, and IL-1 in a wide range of inflammatory disorders.^{11,51,52} Finally, factors other than epithelial disruption may contribute to disease, such as genetics, environmental factors, and alterations in the skin microbiome.^{3,53-55}

Null associations were found for several respiratory, gastrointestinal, and ocular diseases, which we believe can be

explained by several factors. First, the EBT does not state that all EBDs are associated with each other. Additionally, some inflammatory disorders, such as asthma, eosinophilic esophagitis, and food allergy, are frequently reported in younger populations and may be underrepresented in our cohort of adults.⁵⁶⁻⁵⁸ Conditions such as cystic fibrosis and glaucoma have strong genetic components.⁵⁹ Diseases such as gastroesophageal reflux disease (GERD), Barrett esophagus, and diverticulosis, although associated with breaches in the epithelial barrier, often require other permissive conditions in addition to immune sensitization, including gastric reflux (GERD and Barrett esophagus) and diet and lifestyle risk factors (diverticulosis).^{60,61} The complexity of predisposing conditions for these diseases may complicate their associations with seborrheic dermatitis-related epithelial barrier dysfunction. For diseases like uveitis, although some cases are immune-driven, a significant portion also arise from infectious etiologies.⁶² It is reasonable to believe that epithelial barrier dysfunction at the skin surface could lead to antigen sensitization that drives immune-mediated uveitis, and vice versa. However, antigen sensitization is not likely to be as strongly implicated in the development of infectious uveitis. All of the above factors could lead to reduced effect sizes between seborrheic dermatitis and EBDs. Thus, future studies investigating the directional associations between seborrheic dermatitis and EBDs may be warranted to better understand mechanisms of disease progression.

We found that seborrheic dermatitis was associated with several conditions that served as negative controls in our study, including hand fracture, appendicitis, influenza, and astigmatism. However, as defined a priori, these associations were clinically insignificant, and the statistical significance was likely associated with the large size of our sample. We also performed a sensitivity analysis for dermatologic diseases using a subcohort of patients who had at least 1 dermatologist visit. Results from this analysis suggest that a clinically insignificant association exists between seborrheic dermatitis and the sebaceous cyst negative control and that seborrheic dermatitis was associated with AD, alopecia areata, contact dermatitis, psoriasis, rosacea, and CSU (eTable 8 in Supplement 1). These results indicate that these associations with seborrheic dermatitis are unlikely to be due to surveillance or diagnostic bias alone.

Our results were robust against sensitivity analyses investigating the effect of adjustment for a concurrent diagnosis of AD or psoriasis; exclusion of individuals with AD or psoriasis; omission of age, sex, division, time in cohort, and number of visits covariates; requiring a seborrheic dermatitis diagnosis to be defined by seborrheic dermatitis codes logged at 2 separate encounters; and accounting for diagnostic bias in dermatologic diseases. Of the covariates, number of visits had the largest impact on the effect size (Table 2), which is expected because increased clinical encounters allow greater opportunity for disease states to evolve and to be diagnosed. Overall, the sensitivity analyses support the robustness of our findings and reaffirm the importance of adjusting for the number of visits to mitigate bias related to diagnostic opportunity.

Strengths and Limitations

Our study has several strengths. This study included a large population of more than 20 million individuals, which allowed us to observe associations between many diseases in a significant portion of the US population. Additionally, we followed up patients longitudinally in the Optum CDM database from January 1, 2016, through June 30, 2022, resulting in up to 5.5 years of longitudinal follow-up. Patients in our cohort also represented a diverse population in terms of age, sex, and geographic location in the US.

Our study also has several limitations. The first limitation is potential ascertainment bias. Because Optum CDM is an administrative claims database, our study cohort excludes uninsured populations and healthy individuals who do not regularly see a medical professional. Additionally, follow-up with patients is constrained by a need for continuous enrollment within an insurance plan, with gaps in coverage terminating the follow-up period, which may lead to a decrease in effect sizes. Moreover, a limitation of a claims database is the lack of consistent follow-up. Another limitation of our analysis was a lack of validated codes for many of the EBDs we studied. Furthermore, there is a possibility of unmeasured confounding; we mitigate this limitation by calculating E-values in Table 2, which range in value from 1.47 to 8.51 for clinically significant associations. This range represents a large amount of unmeasured confounding that would be needed to explain away the associations, which is unlikely to exist. Given that our results were adjusted for common confounders, including age, sex, geographic location, and health care utilization,

we believe that these E-values demonstrate reasonable robustness of our findings.^{46,47}

Conclusions

This retrospective cohort study found that seborrheic dermatitis, a common EBD of the skin, is associated with other EBDs that originate at various epithelial barriers, including skin, respiratory, gastrointestinal, and ocular surfaces. Although the pathophysiology of seborrheic dermatitis remains unknown, these findings support the role of the EBT model in mediating EBDs at a particular epithelial barrier (eg, skin) and at other types of epithelial barriers (eg, gastrointestinal, respiratory, and ocular). We also found negative associations between seborrheic dermatitis and COPD and pulmonary hypertension, as well as null associations with several EBDs. We hypothesize that these results may arise from variations in epithelial barrier physiology; differing inflammatory mechanisms; and the influence of other factors, such as genetics, environment, complex physiologic etiologies, and skin microbiota, on EBD outcomes. The results both support and encourage further evaluation of the EBT model in the pathogenesis of EBDs. Future studies can be conducted to investigate the temporal relationship between seborrheic dermatitis and EBDs and to explore the underlying molecular mechanisms linking seborrheic dermatitis to EBDs, which will better characterize the role of the EBT model in disease pathogenesis.

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Concept and design: Meng, Berna, Shin, Margolis.
Acquisition, analysis, or interpretation of data: Meng, Berna, Hoffstad, Takeshita, Shin, Chiesa Fuxench.

Drafting of the manuscript: Meng, Berna.
Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Meng, Berna, Shin.

Administrative, technical, or material support: Hoffstad.

Supervision: Chiesa Fuxench.

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