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Antibiotic Exposure, Infection, and the Development of Pediatric Psoriasis:

A Nested Case-Control Study

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Abstract

IMPORTANCE—Antibiotics disrupt human microbiota and have been associated with several pediatric autoimmune diseases. Psoriasis activity has been linked to group A streptococcal and viral infections.

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OBJECTIVE—To determine whether antibiotic exposure and infections are independently associated with incident psoriasis in children.

DESIGN, SETTING, AND PARTICIPANTS—This nested case-control study used data from the Health Improvement Network database, a population-representative electronic health records database from the United Kingdom, from June 27, 1994, through January 15, 2013. Data were analyzed from September 17, 2014, through August 12, 2015. Children aged 1 to 15 years with newly diagnosed psoriasis (n = 845) were compared with age- and sex-matched controls (n = 8450) randomly chosen at the time of psoriasis diagnosis from general practices with at least one case, excluding children with immunodeficiency, inflammatory bowel disease, and juvenile arthritis.

EXPOSURES—Systemic antibacterial prescriptions and infections of the skin and other sites within 2 years before psoriasis diagnosis.

MAIN OUTCOMES AND MEASURES—Incident psoriasis as determined by validated diagnostic codes. The association of antibiotic exposure and infections with incident psoriasis was determined by conditional logistic regression, adjusting for confounders.

RESULTS—After adjusting for matching, country, socioeconomic deprivation, outpatient visits, and infections within the past 2 years, antibiotic exposure in the last 2 years was weakly associated with incident psoriasis (adjusted odds ratio [aOR], 1.2; 95% CI, 1.0–1.5). The associations for infections of skin (aOR, 1.5; 95% CI, 1.2–1.7) and other sites (aOR, 1.3; 95% CI, 1.1–1.6) were similar. Untreated nonskin infections (aOR, 1.5; 95% CI, 1.3–1.8) but not antibiotic-treated nonskin infections (aOR, 1.1; 95% CI, 0.9–1.4) were associated with psoriasis. Results were similar when using a lifetime exposure window. Different classes of antibiotics and age of first antibiotic exposure were also not associated with psoriasis. The findings did not substantively change when excluding periods of varying length before diagnosis.

CONCLUSIONS AND RELEVANCE—Infections are associated with the development of pediatric psoriasis, but antibiotics do not appear to contribute substantially to that risk.

Psoriasis is a chronic autoimmune disease that affects approximately 4 in 1000 children.[1,2] The pathogenesis of psoriasis is incompletely understood but likely involves genetic, immunologic, and environmental factors.[3] Infections may contribute to the development of psoriasis. For instance, individuals with guttate psoriasis frequently have antecedent group A streptococcal infection,[4,5] even though antistreptococcal treatment does not change psoriatic outcomes.[6] Various viruses have been linked to the development or worsening of psoriatic disease.[7–9]

Medications compose another class of reported triggers and exacerbating factors for psoriasis. Among drugs linked to psoriasis are antibiotics, including tetracyclines, mostly on the basis of older case reports and one survey-based study that lacked rigorous methods.[10–12] More recent studies[13–15] have found an association between childhood antibiotic use and 2 related pediatric autoimmune diseases: inflammatory bowel disease (IBD) and juvenile idiopathic arthritis (JIA). Antibiotics disrupt human microbiota, and microbial disturbance has been implicated in the pathogenesis of pediatric IBD and JIA.[16,17] Intestinal microbial disturbance has also been recently observed in adults with psoriasis and

psoriatic arthritis compared with unaffected adults.[18] Furthermore, psoriatic lesions contain abnormal bacterial populations compared with healthy skin, raising the hypothesis that cutaneous microbial disturbance may contribute to psoriasis pathogenesis.[19] No study has examined the connection between antibiotic use and psoriasis in a large pediatric population. We hypothesized that antibiotic use and infections were independently associated with the development of childhood psoriasis in a dose- and time-dependent manner.

Methods

Study Design and Data Source

We performed a nested case-control study using The Health Improvement Network (THIN), a population-representative electronic health records database from more than 550 general practices across the United Kingdom,[20] using methods similar to our previous study on antibiotics and JIA.[15] Nested case-control designs efficiently produce unbiased estimates of incidence rate ratios.[21] THIN contains anonymized patient data on demographics, diagnoses, referrals, and outpatient prescriptions by general practitioners (GPs) collected during routine primary care. This study of anonymized data was exempted by the University of Pennsylvania Institutional Review Board and approved by THIN's scientific review committee. This study included data from June 27, 1994, through January 15, 2013. THIN has been validated for pharmacoepidemiologic research in several diseases,[22] including psoriasis in adults.[2] Data were analyzed from September 17, 2014, through August 12, 2015.

Participant Selection

Eligible participants were 1 to 15 years old and registered within 3 months after birth to capture lifetime outpatient prescriptions. Cases were defined by the first psoriasis diagnosis using an established list of diagnostic Read codes (analogous to *International Classification of Diseases, Ninth Revision*, codes).[2] We used secondary case definitions to improve diagnostic specificity, consisting of the psoriatic code plus (1) psoriatic medication (eTable 1 in the Supplement) or (2) dermatology referral. Children with prior IBD, immunodeficiency, or JIA were excluded.

We matched each case at the time of diagnosis to 10 controls by age and sex without prior psoriasis or exclusion diagnosis, using incidence density sampling. Controls were randomly selected from practices with at least one child diagnosed as having psoriasis.

Exposure and Covariate Data

The primary exposures were systemic antibacterial prescriptions and infections from THIN registration to the index date (defined below). We categorized infections as skin related, which early psoriasis might mimic, or not skin related, using Read codes (Table 1). We classified infections as treated if antibiotics were prescribed within 1 week. Additional analyses categorized antibiotics by class and spectrum of coverage (Table 1).[13] Nonbacterial antimicrobials (eg, antiviral, antimalarial) were analyzed for comparison.

We anticipated protopathic bias whereby early psoriasis symptoms would sometimes be treated as skin infections. To exclude the most likely period of psoriasis misdiagnosis from

analyses, we chose the primary index date empirically at the time before psoriasis diagnosis when GPs began reporting more dermatitis and/or skin lesions in cases relative to controls.

Potential confounders were demographic variables, comorbidities, maternal autoimmunity, and other clinical factors, such as hospitalization and number of outpatient visits within 2 years before the index date (Table 1). We matched participants to their mothers using an algorithm described previously.[15]

Statistical Analysis

Using conditional logistic regression to account for matching, we estimated the association of antibiotic prescription and history of infection (stratified as skin and nonskin) with psoriasis by using odds ratios (ORs) with 95% CIs. Multivariable models included all 3 primary exposure variables and initially all covariates associated with psoriasis in univariable analysis with $P < .20$. In multivariable models, we retained those variables that were independently associated with psoriasis ($P < .05$) or changed the OR for antibiotic exposure by 10% or more. We compared adjusted ORs (aORs) of variables within the same model using linear combination to determine whether they significantly differed from each other. We omitted variables with 10% or more missing data from multivariable models. The primary analysis examined antibiotics prescribed within 2 years before the index date because microbial changes may sometimes persist for more than 1 year after antibiotic exposure.[23] This time window also accommodated uncertainty about preclinical psoriasis onset.

To distinguish further between the effects of antibiotics and infections, additional models compared the associations of treated and untreated infections. We specifically evaluated antibiotic use for upper respiratory tract infections because these infections frequently do not require antibiotic use. Thus, they offer the opportunity to examine people with similar infections but treated and not treated with antibiotics. Secondary analyses studied antibiotic coverage and drug class, the timing of first and last antibiotics prescribed, and lifetime exposure windows.

We performed multiple sensitivity analyses. We examined assumptions about antibiotic timing and protopathic bias by moving the index date from 0 to 36 months before diagnosis. Because THIN lacks inpatient medication data, we repeated analyses assuming antibiotics were received during hospitalizations within 1 week of infections. Additional analyses focused on cases with 2 or more psoriasis Read codes for improved diagnostic predictive value.[2] Considering possible confounding by local practice patterns and unmeasured environmental factors, we repeated analyses after matching cases and controls by practice. To further consider confounding from infection, we compared the rate of infections between cases and controls not prescribed antibiotics.

We used STATA/IC statistical software, version 12.1 (StataCorp), for all analyses. Hypothesis tests were 2-sided with a type I error of 0.05.

Results

Characteristics of the Study Population

We identified 845 eligible cases among 894 children with psoriasis in a population of 454 463 children followed up for 3.1 million person-years. Guttate psoriasis was the most common variant reported (18.9%) although most cases had nonspecific psoriasis diagnoses (eTable 1 in the Supplement). Psoriasis incidence was 29 per 100 000 person-years, with increasing incidence and female predominance at older ages (Figure). Cases more likely lived in northern countries ($P < .001$) and in areas with more socioeconomic deprivation ($P < .001$) (Table 1). Cases more commonly had a history of infections of skin and other sites, as well as more prior infections than controls ($P < .001$). Cases also had more outpatient visits within 2 years of the index date (defined below) ($P < .001$). Mothers of cases more likely had autoimmune diseases ($P < .001$), particularly psoriasis; maternal psoriasis was strongly associated with psoriasis (unadjusted OR, 4.0; 95% CI, 3.2–5.1). Tobacco use, but not cesarean delivery, was more common among cases' mothers, but the data were missing for 11.4% and 42.4% of cases and 12.6% and 39.8% of controls, respectively.

The GPs noted more dermatitis and/or skin lesions among cases starting 12 months before psoriasis diagnosis, a trend accelerating 4 months before diagnosis (eFigure 1 in the Supplement). In contrast, monthly reporting of dermatitis and/or skin lesions for controls did not change during the same period. On the basis of these trends, we selected a primary index date 12 months before psoriasis diagnosis, excluding subsequent antibiotic prescriptions and infections to limit capturing treatment of early psoriasis as infection.

Association of Antibiotics, Infections, and Psoriasis

Receipt of an antibiotic prescription within 2 years of the index date was strongly associated with psoriasis in unadjusted models (OR, 1.9; 95% CI, 1.6–2.2). However, after adjusting for prior infection and number of outpatient visits within 2 years (both strong confounders), country, and socioeconomic status, antibiotic exposure was only weakly associated with psoriasis (aOR, 1.2; 95% CI, 1.0–1.5) (Table 2). The associations of prior infections with psoriasis were similar in the same model (skin infection: aOR, 1.5; 95% CI, 1.2–1.7; nonskin infection: aOR, 1.3; 95% CI, 1.1–1.6).When considering the time-frame back to birth, the association of antibiotic exposure with psoriasis was similar to that of skin infections. The association between antibiotics and psoriasis was similar in those with and without prior infection (eTable 2 in the Supplement). Additional adjustment for maternal history yielded similar results (eTable 2 in the Supplement). Treated and untreated skin infections had associations with psoriasis of equal magnitude (Table 3). In contrast, untreated non-skin infections in the last 2 years were more strongly associated with psoriasis than treated infections ($P = .02$ for comparison of aORs) (Table 3).

Secondary analyses of cases with documented treatment for psoriasis produced similar results to the primary analyses (eTable 2 in the Supplement). Analyses limited to cases referred to dermatologists (n = 201) yielded estimates that suggested a slightly stronger association of antibiotic exposure and skin infections with psoriasis compared with the

primary analysis; however, aORs for antibiotics and both skin and nonskin infections did not differ significantly from one another (eTable 2 in the Supplement).

When considering exposure timing, cases were as likely to have recent antibiotic prescriptions as untreated skin or nonskin infections during the same interval (Table 4). Age of first antibiotic exposure did not relate to psoriasis diagnosis ($P = .39$). Analyses of antibiotic coverage and specific drug classes resembled those for overall antibiotic exposure, with weak or no associations with psoriasis (eTable 2 in the Supplement). Nonbacterial antimicrobials were not associated with psoriasis.

Sensitivity Analyses

When the index date moved from 4 to 36 months before psoriasis diagnosis, the effects of antibiotics remained comparable to skin and nonskin infections, although nonskin infections were not associated with psoriasis when the index date was the date of diagnosis (eFigure 2 in the Supplement). With each study period considered, the effects of untreated infections were similar to or greater than the effects of treated infections. Of note, the ORs for treated and untreated skin infections increased as the index date moved toward psoriasis diagnosis, possibly reflecting antibiotic treatment of early psoriasis as possible infection (protopathic bias). Findings were similar when assuming antibiotic receipt during hospitalization for infection, when analyzing cases with 2 or more psoriasis codes, and when comparing cases and controls matched by practice (eTable 3 in the Supplement). Skin infections were associated with psoriasis in unexposed participants (aOR, 1.5; 95% CI, 1.1–2.1; $P = .02$). When analyzing the original and practice- matched data sets jointly to protect against type I error, no infection type was consistently associated with psoriasis. In exploratory analyses using the date of psoriasis diagnosis as the index date, antibiotic-treated pharyngitis was associated with guttate psoriasis (aOR, 1.9; 95% CI, 1.0–3.6) but not other psoriasis variants (aOR, 1.0; 95 % CI, 0.7–1.4). In the same models, antibiotic-untreated pharyngitis was not associated with guttate or nonguttate psoriasis.

Discussion

We found that antibiotics were no more strongly associated with newly diagnosed psoriasis in children than infections managed without antibiotics. These findings were consistent across multiple analyses of various types of infections, drug classes, and exposure windows. Among our many analyses, only those limited to cases referred to dermatologists revealed a slightly stronger effect of antibiotics compared with infections. However, the imprecise estimates from this small model (<25% of the overall cohort) did not significantly differ from one another. Overall, our findings support prior literature that infections may play a role in the development of psoriasis[5,7,9] but suggest that antibiotics do not substantially, independently contribute to this risk.

Previous studies[10–12] linking psoriasis and antibiotics (particularly tetracyclines) were either uncontrolled case reports or observational studies in adults based on self-report, a design susceptible to recall bias. Few children in our cohort were prescribed tetracyclines, limiting our ability to study this antibiotic class. However, our results suggest that an apparent association between antibiotics and psoriasis more likely reflects confounding from

infections, at least in children. Older literature analogously suggested a link between pediatric asthma and antibiotic use,[24] but more recent studies[25,26] implicate respiratory tract infections and familial risk factors as principal drivers of this association. In our study, adjustment for maternal history of psoriasis and other autoimmune diseases did not change results.

Using analogous methods, we and others have previously reported associations between childhood antibiotic exposure and pediatric autoimmune diseases that overlap clinically with psoriasis, namely, IBD and JIA.[13–15] One proposed explanation for those findings is antibiotic-induced disruption of microbiota.[27] Microbial disruption has been reported in pediatric IBD and 1 form of JIA.[16,17] Cesarean delivery is another potential source of early-life microbial disturbance.[28] A recent population-based study[29] suggested that cesarean delivery was a risk factor for certain pediatric autoimmune diseases, including IBD and JIA, but not for psoriasis. Those findings parallel our own in suggesting that factors disrupting microbiota may not play the same role in psoriasis pathogenesis as in clinically related pediatric autoimmune diseases.

Other studies[5,9] have suggested that infections, including group A streptococcus and viruses, may trigger psoriasis. We found that untreated infections not affecting the skin, presumably viral infections, were more strongly associated with psoriasis than antibiotic-treated infections. Although respiratory tract infections have long been described in connection with psoriasis in children, our case-control design was more rigorous than many previous studies[30–32] whose conclusions were based on patient and family report in uncontrolled case series and single-arm cohorts. Our data also support previous research linking group A pharyngitis specifically with guttate psoriasis.[4,5] In addition, skin infections were associated with psoriasis in our study. It is unclear to what extent this finding reflects misdiagnosis of early psoriasis as infection, misdiagnosis of an infection-related skin diseaseas psoriasis (eg, molluscum contagiosum dermatitis, pityriasis rosea), or whether skin infections may trigger psoriasis in children. Previous work[19,33] has found different microbiota in psoriatic lesions compared with healthy skin, including increased abundance of streptococcal and staphylococcal species. The functional significance of these differences remains unclear; some hypothesize that abnormal cutaneous immune responses to skin-dwelling bacteria lead to psoriatic disease.[34] Another potential mechanism linking infections and psoriasis are endogenous cutaneous antimicrobial molecules that trigger loss of immune tolerance and production of proinflammatory cytokines.[35] Genetic differences may also explain how some children may develop psoriasis after infections. Individuals with psoriasis triggered or worsened after upper respiratory tract infections more likely carried interleukin 20 polymorphisms in one study.[36] Another study found that young children with psoriasis more commonly had interleukin 22 promoter variants associated with higher circulating levels of this proinflammatory cytokine important in epithelial host defense.[37]

An alternative explanation for an association between infections and pediatric psoriasis is that altered immunity in children with psoriasis could render them more susceptible to infections earlier in life. Severe psoriasis has been observed in people with advanced human immunodeficiency virus disease and other immunodeficiencies.[8,38] We noted a decreasing association between nonskin infections and psoriasis as the index date moved to the date of

diagnosis, arguing against the hypothesis of disease-associated susceptibility to infection. Ascertainment bias, whereby an unrelated infection brings a person's psoriasis to medical attention, was unlikely to have explained the results because our primary analyses excluded infections within 1 year before GPs diagnosed psoriasis.

Obesity may disproportionately affect individuals with psoriasis.[39,40] Some evidence suggests that obesity may predispose children to psoriasis,[41] although the pathophysiology of this association is poorly understood. Of interest, antibiotic exposure and microbial disruption may play a role in the development of obesity in children.[42] If obesity were on the causal pathway between microbial disturbance and psoriasis, antibiotics could theoretically play a role in the development of psoriasis during a longer time horizon in susceptible individuals. We did not investigate the association of antibiotics, obesity, and psoriasis in this study because most children lacked body mass index data.

Other environmental factors have been suggested as linked to psoriasis in children. In one report,[43] children with newly diagnosed psoriasis had an increased risk of tobacco exposure. Smoking has been more clearly associated with the development of psoriasis in adults.[44] Our study suggested a possible association with maternal smoking although we did not evaluate this in detail because of missing data. Sunlight exposure could also relate to psoriasis risk by stimulating the production of vitamin D, which is an important treatment for psoriasis.[45] In our study, those living in more northern countries of the United Kingdom were more likely to develop psoriasis, which could reflect the risk from lower levels of natural sunlight exposure and endogenous vitamin D production.

Our study has several strengths. The age- and sex-related incidence of psoriasis with female predominance in our cohort was consistent with previous population-based studies in children.[46,47] Use of secondary case definitions to improve diagnostic specificity yielded consistent results. In addition, our findings were robust to multiple secondary and sensitivity analyses designed to test study assumptions and to consider potential sources of bias.

This study also has certain limitations. Several factors may have biased results toward the null: evaluation of antibiotic prescriptions rather than dispensing and consumption data, diagnostic misclassification of psoriasis by GPs, and adjustment for clinic visits if this variable were on the causal pathway between antibiotics and psoriasis. However, even unadjusted effects of antibiotics were similar to those of infections, and infections may also be underreported in a clinical database because not all infections come to medical attention. Psoriasis has been validated in THIN but only in adults.[2] Because most children in this study were 10 years or younger, we were unable to examine the association between antibiotics and psoriasis in older children and adults, to whom our findings may not apply. Findings from the United Kingdom may also not generalize to other countries with distinct ethnic populations. We also could not evaluate the association between antibiotics and pediatric psoriatic arthritis because we excluded children with preexisting JIA.

Conclusions

Our study reveals that infections are associated with the development of pediatric psoriasis in a large general pediatric population, but antibiotics do not appear to contribute independently to disease risk. Infections may play a role in triggering psoriatic disease in children, perhaps through alterations in skin microbiota or exaggerated immunologic responses. Although psoriasis in children shares clinical and genetic features with IBD and JIA, which have been associated with antibiotic use, the mechanisms underlying the initiation of these autoimmune diseases may differ.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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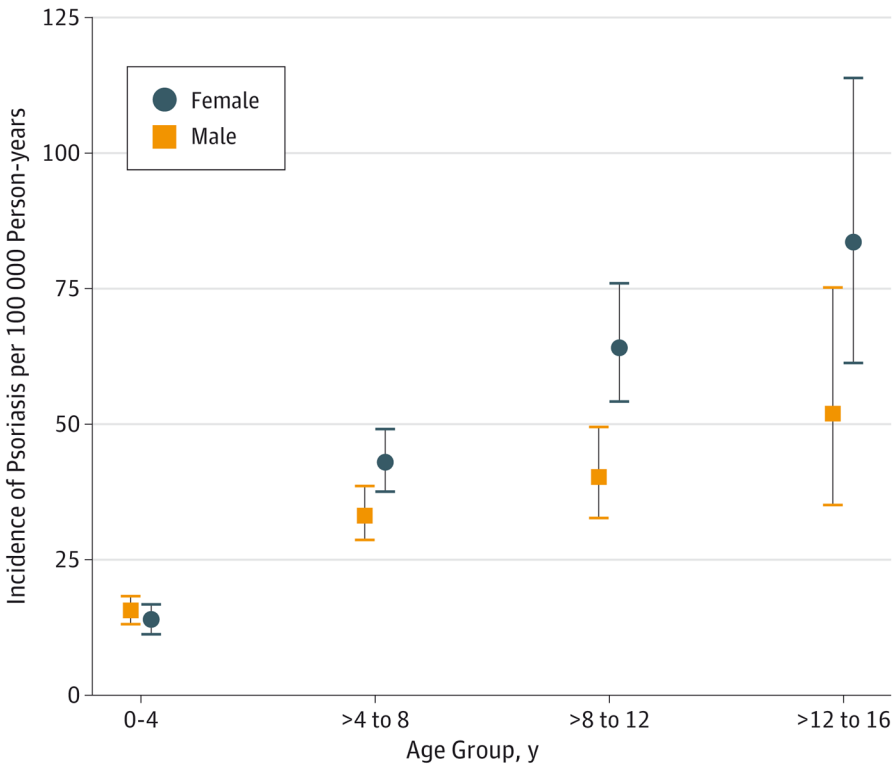

Figure.

Incidence of Psoriasis by Age and Sex in the Source Population

The incidence of pediatric psoriasis in the study's source population in The Health Improvement Network (THIN) is presented across 4 age groups stratified by sex. Error bars indicate 95% CIs.

Table 1

Characteristics of the Study Population[a]

Characteristic	Cases (n = 845)	Controls (n = 8450)	*P* Value[b]
Demographics			
Female sex	465 (55.0)	4650 (55.0)	…[c]
Age, median (IQR), y	6 (4–8)	6 (4–8)	…
Age category, y			
1–5	366 (43.3)	3660 (43.3)	…
6–10	367 (44.4)	3670 (44.4)	
11–15	112 (13.3)	1120 (13.3)	
Country of origin			
England	660 (78.1)	7189 (85.1)	<.001[d]
Northern Ireland	62 (7.3)	325 (3.9)	
Scotland	78 (9.2)	545 (6.5)	
Wales	45 (5.3)	391 (4.6)	
Townsend index[e]			
1	179 (21.2)	2157 (25.5)	<.001[d]
2	161 (19.1)	1657 (19.6)	
3	159 (18.8)	1596 (18.9)	
4	173 (20.5)	1578 (18.7)	
5	146 (17.3)	1186 (14.0)	
Missing	27 (3.2)	276 (3.3)	
Comorbidities			
Personal autoimmunity[f]	4 (0.5)	16 (0.2)	
Celiac disease	0	8 (0.1)	.10[g]
Thyroid disease	1 (0.1)	4 (<0.1)	
Type 1 diabetes mellitus	3 (0.4)	5 (0.1)	
Any infection[f]	754 (89.2)	7185 (85.0)	<.001
Any skin infection[f]	475 (56.2)	3838 (45.4)	<.001
External genitourinary	65 (7.7)	444 (5.3)	.003
Herpes simplex	18 (2.1)	114 (1.4)	.07
Molluscum contagiosum	6.2 (7.3)	516 (6.1)	.15
Tinea	67 (7.9)	341 (4.0)	<.001
Wart	90 (10.7)	609 (7.2)	<.001
Varicella	194 (23.0)	1679 (19.9)	.03
Other viral exanthem	50 (5.9)	311 (3.7)	.001
Other skin and soft-tissue infection	249 (29.5)	1943 (23.0)	<.001
Any other infection[f]	736 (87.1)	6946 (82.2)	<.001

Characteristic	Cases (n = 845)	Controls (n = 8450)	*P* Value[b]
Upper respiratory tract	674 (79.8)	6317 (74.8)	<.001
Lower respiratory tract	327 (38.7)	2399 (28.4)	<.001
Gastrointestinal	163 (19.3)	1504 (17.8)	.28
Urinary tract	52 (6.2)	395 (4.7)	.05
Other	355 (42.0)	3108 (36.8)	.002
No. of infections, median (IQR)	5 (2–10)	4 (1–8)	<.001
Antibiotic Exposures			
Any antibiotic prescribed	710 (84.0)	6343 (75.1)	<.001
Antianaerobic antibiotics[f]	683 (80.8)	6099 (72.2)	<.001
Penicillins	677 (80.1)	6056 (71.7)	<.001
Broad-spectrum penicillins	109 (12.9)	667 (7.9)	<.001
Metronidazole	4 (0.5)	48 (0.6)	.73
Clindamycin	0	0	…
Other antianaerobic[h]	0	5 (0.1)	…
Nonantianaerobic antibiotics[f]	354 (41.9)	2827 (33.5)	<.001
Cephalosporins	136 (16.1)	946 (11.2)	<.001
Macrolides	254 (30.1)	1988 (23.5)	<.001
Sulfonamides	107 (12.7)	764 (9.0)	<.001
Other nonantianaerobic[h]	6 (0.7)	34 (0.4)	.20
Antimalarial	13 (1.5)	88 (1.0)	.19
Other antimicrobial exposure[i]	72 (8.5)	591 (7.0)	.10
Maternal Variables			
Maternal autoimmunity[f]	150 (19.7)	671 (8.8)	<.001
Arthritis	15 (2.0)	35 (0.5)	<.001
Celiac disease	3 (0.4)	18 (0.2)	.40
Connective tissue disease	2 (0.3)	14 (0.2)	.72
Diabetes	2 (0.3)	25 (0.3)	.81
Inflammatory bowel disease	12 (1.6)	53 (0.7)	.01
Multiple sclerosis	1 (0.1)	10 (0.1)	…
Psoriasis	101 (13.3)	270 (3.5)	<.001
Thyroid disease	26 (3.4)	248 (3.2)	.81
Uveitis	8 (1.1)	33 (0.4)	.04
Maternal smoking	285 (33.7)	2364 (28.0)	.001
Missing maternal smoking data	96 (11.4)	1067 (12.6)	…
Missing maternal data	83 (9.8)	804 (9.5)	…
Other Variables			
Cesarean delivery	119 (14.1)	1224 (14.5)	.77
Missing delivery data	358 (42.4)	3360 (39.8)	…

Characteristic	Cases (n = 845)	Controls (n = 8450)	*P* Value[b]
Hospitalization[f]	104 (12.3)	863 (10.2)	.06
Infection	46 (5.4)	347 (4.1)	.07
Other	71 (8.4)	626 (7.4)	.29
No. of outpatient visits in last 2 years,[j] median (IQR)	5 (2–9)	3 (0–7)	<.001

Abbreviation: IQR, interquartile range.

[a] Data are presented as number (percentage) unless otherwise indicated.

[b] All *P* values were obtained from univariable conditional logistic regression models.

[c] Ellipses indicate data not applicable.

[d] Overall χ^2 test *P* value.

[e] Geography-based deprivation index; higher index score means more deprived.

[f] Some participants had more than one type.

[g] Comparison of main category.

[h] Other antianaerobic antibiotics include tetracyclines, glycopeptides (oral vancomycin), carbapenems, and cefoxitin (all other cephalosporins categorized as nonantianaerobic); other nonantianaerobic antibiotics include fluoroquinolones and all other antibiotic classes.

[i] Other antimicrobial agents, including antifungal, antiviral, and antimycobacterial drugs.

[j] Total outpatient visits per year for 2-year period starting 3 years before psoriasis diagnosis.

Table 2

Association of Antibiotic Prescriptions and Infections With Psoriasis

Variable	Exposed Cases (n = 818)	Exposed Controls (n = 7913)	Unadjusted OR	Adjusted OR[a] (95% CI)	*P* Value
Primary analysis: 2-y exposure window					
Any antibiotic prescription	453	3273	1.9	1.2 (1.0–1.5)	.05
Any skin infection[b]	248	1531	1.8	1.5 (1.2–1.7)	<.001
Any other infection[c]	466	3438	1.9	1.3 (1.1–1.6)	.005
Secondary analysis: lifetime exposure window					
Any antibiotic prescription	686	5946	2.1	1.5 (1.2–1.9)	.002
Any skin infection[b]	465	3616	1.7	1.4 (1.2–1.7)	<.001
Any other infection[c]	712	6515	1.6	1.0 (0.8–1.3)	.86

Abbreviation: OR, odds ratio.

[a] Models adjusted for antibiotics, skin infections, nonskin infections, matching, country, deprivation score, and number of outpatient visits.

[b] Includes external genitourinary, herpes simplex, molluscum contagiosum, tinea, varicella, other acute viral exanthems, warts, and other skin or soft-tissue infections.

[c] Includes upper and lower respiratory tract, gastrointestinal tract, urinary tract, and all other infections.

Table 3

Association of Treated and Untreated Infections with Psoriasis

Exposure Window	Exposed Cases (n = 818)	Exposed Controls (n = 7913)	Unadjusted OR	Adjusted OR[a] (95% CI)	*P* Value
2 Years					
Skin infection,[b] treated	84	495	1.7	1.4 (1.1–1.8)	.02
Skin infection,[b] untreated	190	1184	1.7	1.4 (1.2–1.7)	<.001
Other infection,[c] treated	293	2103	1.6	1.1 (0.9–1.4)	.18
Other infection,[c] untreated	366	2471	2.0	1.5 (1.3–1.8)	<.001
Upper respiratory tract infections					
Any, treated	241	1755	1.5	1.1 (0.9–1.3)	.39
Any, untreated	263	1816	1.7	1.3 (1.1–1.5)	.008
Lifetime					
Skin infection,[b] treated	216	1534	1.5	1.3 (1.1–1.5)	.009
Skin infection,[b] untreated	293	3011	1.6	1.3 (1.1–1.6)	.001
Other infection,[c] treated	573	4782	1.6	1.2 (1.0–1.5)	.03
Other infection,[c] untreated	664	5888	1.6	1.2 (1.0–1.5)	.11
Upper respiratory tract infections					
Any, treated	510	4239	1.5	1.2 (1.02–1.4)	.03
Any, untreated	559	4937	1.4	1.1 (0.9–1.3)	.36

Abbreviation: OR, odds ratio.

[a] Models adjusted for antibiotic-treated infections, untreated infections, matching, country, deprivation score, and number of outpatient visits.

[b] Includes external genitourinary, herpes simplex, molluscum contagiosum, tinea, varicella, other acute viral exanthems, warts, and other skin or soft-tissue infections.

[c] Includes upper and lower respiratory tract, gastrointestinal tract, urinary tract, and all other infections.

Table 4

Effect of Timing of Last Exposure on the Association With Psoriasis

Timing of Last Exposure Before Psoriasis Diagnosis (mo)	Any Antibiotic				Any Untreated Skin Infection[a]				Any Untreated Other Infection[b]			
	Exposed Cases (n = 818)	Exposed Controls (n = 7913)	Adjusted OR (95% CI)[c]	*P* Value	Exposed Cases (n = 818)	Exposed Controls (n = 7913)	Adjusted OR (95% CI)[c]	*P* Value	Exposed Cases (n = 818)	Exposed Controls (n = 7913)	Adjusted OR (95% CI)[c]	*P* Value
Unexposed (reference)	132	1967			426	4902			155	2037		
>24	233	2673	1.3 (1.02–1.7)	.03	202	1827	1.2 (1.01–1.5)	.04	302	3423	1.0 (0.8–1.3)	.80
12–24	131	1088	1.6 (1.2–2.2)	.001	80	536	1.5 (1.2–2.0)	.003	141	1005	1.6 (1.2–2.1)	.001
6–12	110	822	1.9 (1.4–2.5)	<.001	45	297	1.5 (1.1–2.1)	.02	108	611	2.0 (1.5–2.7)	<.001
0–6	212	1363	2.1 (1.6–2.7)	<.001	65	351	1.8 (1.4–2.5)	<.001	112	837	1.5 (1.1–1.9)	.007

Abbreviation: OR, odds ratio.

[a] Includes external genitourinary, herpes simplex, molluscum contagiosum, tinea, varicella, other acute viral exanthems, warts, and other skin or soft-tissue infections.

[b] Includes upper and lower respiratory tract, gastrointestinal tract, urinary tract, and all other infections.

[c] Models adjusted for timing of last antibiotic course, skin infection, nonskin infection, matching, country, and deprivation score.