Prenatal, infantile, and childhood tobacco exposure and risk of pediatric psoriasis in the Danish National Birth Cohort offspring

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Background: Tobacco smoking is implicated in psoriasis among adults.

Objective: To determine whether prenatal, infantile, and childhood tobacco exposure increase risk of pediatric psoriasis.

Methods: Data from Danish National Birth Cohort participants were collected at approximately gestational week 12 and when the children were approximately 6 months and 11 years of age. In total, 25 812 offspring with complete data from the Danish National Birth Cohort were included. We estimated the odds of pediatric psoriasis with tobacco exposure prenatally, from birth to age 6 months (early infancy), and at age 11 years (childhood).

Results: We observed an increased risk of pediatric psoriasis among offspring with prenatal tobacco exposure (adjusted odds ratio [OR], 1.39; 95% confidence interval [CI], 1.06-1.82). An exposure-response relationship was observed for increasing quantities of cigarettes smoked daily (≥16 cigarettes: adjusted OR, 2.92; 95% CI, 1.20-7.10; *P* for trend = .038). The associations with infantile (adjusted OR, 1.17; 95% CI, 0.76-1.79) and childhood (adjusted OR, 1.10; 95% CI, 0.77-1.58) tobacco exposure were attenuated after controlling for prenatal exposure.

Limitations: Outcome status was maternally reported.

Conclusions: Prenatal tobacco exposure may increase the risk of pediatric psoriasis in a monotonic fashion, indicating that smoking may play a causal role in psoriasis pathogenesis. (J Am Acad Dermatol 2020;83:1625-32.)

Key words: cohort; dermatology; epidemiology; pediatric psoriasis; psoriasis; public health; smoking; tobacco.

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Psoriasis is a chronic inflammatory skin disease with an estimated prevalence in industrialized nations of 2% to 3% among adults and 0.7% in the pediatric population.[1,2] It is a multifactorial disease with a strong genetic component, especially the early-onset phenotype.[3-5] Nonetheless, environmental factors such as streptococcal pharyngitis or stressful life events appear to be common disease triggers in the first manifestation.[5,6]

Among the modifiable risk factors for psoriasis in the adult population is active smoking.[3,7-9] Passive tobacco exposure is also significantly associated with a number of disease outcomes in adults[10] and affects numerous health outcomes in offspring of smoking parents.[11,12] Among these is pediatric obesity,[13] a potential risk factor for pediatric psoriasis. To our knowledge, only 2 previous studies have investigated associations between fetal or childhood tobacco exposure and psoriasis in adults—both of which found positive associations.[9,14] Only 1 study has investigated the role of prenatal and childhood tobacco exposure in relation to pediatric psoriasis,[15] and this might be affected by recall bias and residual confounding.

We sought to elucidate the role of prenatal, infantile, and childhood tobacco exposure in pediatric psoriasis, with prospectively collected data, in the case of prenatal and infantile exposure.

CAPSULE SUMMARY

- We found that prenatal tobacco exposure is associated with pediatric psoriasis in a monotonic fashion in a large national Danish birth cohort.
- Tobacco exposure during pregnancy may play a causal role in the development of pediatric psoriasis.

METHODS

Study population and base cohort

Participants were drawn from the Danish National Birth Cohort,[16] a nationwide cohort of pregnant women, recruited from 1996 through 2002 and consisting of 100 415 pregnancies. Informed consent was obtained from participants upon enrolment, and the study was approved by the Danish Data Protection Agency through the joint notification of the Faculty of Health and Medical Sciences at the University of Copenhagen (Sund-2017-09), according to Danish regulations. Additional information regarding the study population is available through a previous publication.[17]

Briefly, information on lifestyle and environmental factors potentially associated with offspring health was collected through 4 prenatal and postnatal telephone interviews at target ages gestational weeks (GW) 12 and 30 and child ages 6 and 18 months.[16] The parent-child dyads were then invited for follow-up at 7, 11, and 18 years.

In the 11-year follow-up wave, DNBC mothers or fathers were invited to respond to a comprehensive online questionnaire regarding their offspring's health. Version 2 of the questionnaire included an item regarding offspring psoriasis.

We restricted our study population to offspring whose mothers had responded to interview 1 (GW 12), interview 3 (child age 6 months), and version 2 of the 11-year follow-up, as well as to each of the primary smoking questionnaire items considered in each of these 3 follow-up waves.

Offspring psoriasis classification

Data on offspring psoriasis were obtained from an 11-year follow-up questionnaire for mothers of DNBC offspring. Participants were identified as offspring with psoriasis if their mothers responded affirmatively to the question of whether the child had ever had "an outbreak of the disease psoriasis (p. 24)."[18]

Environmental tobacco exposure

Tobacco exposure was evaluated based on maternal reports at the 3 aforementioned time points, 1 prenatal (interview 1, GW 12), 1 in early infancy (interview 3, child age 6 months), and 1 at the 11-year follow-up (version 2 of the 11-year questionnaire). For each period, tobacco exposure was categorized dichotomously. For the first 2 waves, exposure was based on whether the mother had smoked within the specified time period (yes/no): during the first 12 GWs in interview 1 and in early infancy in interview 3. In the 11-year follow-up, offspring were classified as currently unexposed (never- and former-smoking responding parent) and exposed (light- and regular-smoking responding parent). Quantity of cigarettes smoked daily during the prenatal period for mothers reporting current smoking at time of the interview was assessed by using maternally reported data from interview 1. Participants were categorized into ordinal groups of approximately 5 additional cigarettes smoked daily (0, 1-5, 6-10, 11-15, 16+). Finally, prenatal nicotine exposure from nicotine

Abbreviations used:

CI: confidence interval
DNBC: Danish National Birth Cohort
GW: gestational week
NRT: nicotine replacement therapy
OR: odds ratio

replacement therapy (NRT), such as gum and patches, was also assessed with data from interview 1 and categorized dichotomously, according to exposure within approximately the first 12 GWs. Analyses of prenatal and infantile tobacco exposures were longitudinal (cohort analyses), whereas analysis of tobacco exposure in the 11-year follow-up was cross-sectional.

Covariates

Directed acyclic graphs were constructed to determine potential confounders in a causal model. Maternal alcohol intake was not considered a potential confounder, because there is no indication that similar effects of alcohol exposure on psoriasis risk would occur in fetuses as in adults, the drinking and smoking patterns during pregnancy in our population appear to differ by socio-occupational position, and associations between alcohol intake and psoriasis in adults may be confounded by smoking status, rather than vice versa.[19] A minimally sufficient adjustment set of covariates was selected for prenatal tobacco exposure, including highest parental socio-occupational status in the household, according to the Danish version of the International Standard Classification of Occupations, v1.0:1988[20] (high-grade professional, low-grade professional, skilled worker, unskilled worker, student, economically inactive, and unclassified); maternal age at birth from the Danish Medical Birth Registry (<25, 25-29, 30-34 and ≥ 35 years old); and maternal psoriasis (self-reported, doctor diagnosed, and reported in interview 1). For infantile and childhood tobacco exposure, we additionally adjusted for prenatal exposure. Psoriatic predisposition and sex were considered potential effect modifiers, based on evidence that the effects of tobacco on psoriasis may differ by genetic predisposition and biological sex.[21]

Statistical analyses

We performed univariable and multivariable logistic regression analyses to estimate crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) of offspring psoriasis by each tobacco exposure. Additional analyses were conducted modeling prenatal tobacco exposure by ordinal categories of number of cigarettes smoked daily by the mother.

In addition to the crude models, 3 adjusted models were constructed in analyses of each exposure. In adjusted model 1, we controlled for the confounding variables socio-occupational position and maternal age at birth. Because of uncertainty in the causal links and temporal relationships between maternal psoriasis and smoking prenatally and in early infancy, we constructed an adjusted model (adjusted model 2) in which we additionally included maternal psoriasis. Finally, to isolate the explanatory effect of adjusting for previous tobacco exposure in the analyses of infantile and childhood tobacco exposure, we constructed a final model (adjusted model 3) in which we also included prenatal exposure.

A priori supplementary analysis of nicotine exposure from prenatal use of NRT was conducted with the same models for adjustment used for tobacco exposure. Additionally, a post hoc analysis of patterns of fetal exposure to NRT and/or tobacco was conducted. Categories of exposure were classified into the following patterns: no use during pregnancy, quit smoking before interview 1 without NRT, quit smoking before interview 1 with NRT, constant smoking without NRT, and constant smoking with NRT.

We conducted complete case analyses. Robust standard errors were applied to the logistic regression analyses to account for siblingship, because mothers could contribute to the cohort with multiple births or multiple pregnancies.

We additionally tested whether maternal psoriasis status or sex of the offspring might be effect modifiers, using the likelihood ratio test. Likelihood ratio test results of a P value of less than .10 for maternal psoriasis and less than .05 for sex were considered in stratified analyses. Because the number of observations in interaction terms for maternal psoriasis and tobacco exposure were low, we deemed the aforementioned significance level acceptable so as to reduce the probability of making a type II error. A test of trend score was estimated for quantity of cigarettes smoked in the prenatal period for those reporting current smoking at the first interview, using the extended Mantel-Haenszel chi-square test of linear trend.

In sensitivity analyses, we included available cases with questionnaire item nonresponse(s).

Statistical analyses were performed using Stata statistical software, version 15 (StataCorp, College Station, TX).

Table I. Baseline demographic characteristics of the base study population by prenatal, infantile, and childhood tobacco exposure

	Prenatal tobacco exposure, n (%)		Infantile tobacco exposure, n (%)		Childhood tobacco exposure, n (%)	
Characteristics	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**
Total	20 514 (100)	5298 (100)	22 687 (100)	3125 (100)	22 388 (100)	3424 (100)
Sex						
Male	10 237 (49.9)	2549 (48.1)	11 292 (49.8)	1494 (47.8)	11 130 (49.7)	1656 (48.4)
Female	10 277 (50.1)	2749 (51.9)	11 395 (50.2)	1631 (52.2)	11 258 (50.3)	1768 (51.6)
Maternal age at birth, y						
<25	1792 (8.7)	745 (14.1)	2109 (9.3)	428 (13.7)	2026 (9.0)	511 (14.9)
25-29	8669 (42.3)	2164 (40.9)	9617 (42.4)	1216 (38.9)	9413 (42.0)	1420 (41.5)
30-34	7441 (36.3)	1735 (32.8)	8122 (35.8)	1054 (33.7)	8070 (36.0)	1106 (32.3)
≥35	2612 (12.7)	654 (12.3)	2839 (12.5)	427 (13.7)	2879 (12.9)	387 (11.3)
Maternal psoriasis						
Yes	470 (2.3)	230 (4.3)	558 (2.5)	142 (4.5)	553 (2.5)	147 (4.3)
No	20 044 (97.7)	5068 (95.7)	22 129 (97.5)	2983 (95.5)	21 835 (97.5)	3277 (95.7)
Socio-occupational status						
High-grade professional	5681 (27.7)	903 (17.0)	6105 (26.9)	479 (15.3)	6021 (26.9)	563 (16.4)
Low-grade professional	7392 (36.0)	1625 (30.7)	8128 (35.8)	889 (28.5)	8038 (35.9)	979 (28.6)
Skilled worker	4950 (24.1)	1615 (30.5)	5552 (24.5)	1013 (32.4)	5458 (24.4)	1107 (32.3)
Unskilled worker	1953 (9.5)	980 (18.5)	2293 (10.1)	640 (20.5)	2274 (10.2)	659 (19.2)
Student	426 (2.1)	133 (2.5)	488 (2.2)	71 (2.3)	478 (2.1)	81 (2.4)
Economically inactive	79 (0.4)	34 (0.6)	87 (0.4)	26 (0.8)	84 (0.4)	29 (0.9)
Unclassified	33 (0.2)	8 (0.2)	34 (0.2)	7 (0.2)	35 (0.2)	6 (0.2)

RESULTS

Of 90 986 invitations sent to mothers for the 11-year follow-up, 36 003 responses to version 2 of the online questionnaire were collected. Because of loss to follow-up at one of the follow-up waves or response to version 1 rather than version 2 of the online questionnaire, 63 624 offspring were excluded from our study. In total, 25 812 complete cases, out of the 27 362 participants whose mothers had responded to all 3 follow-up waves, were identified. Socio-occupational status and maternal age at birth were associated with tobacco exposure at each follow-up wave, so that inverse social and age gradients could be observed for each exposure (Table I). In our population for analyses, we identified 281 offspring with psoriasis (prevalence of 1.1%).

Prenatal tobacco exposure as a whole appears to moderately increase the risk of pediatric psoriasis at the exposure levels observed in our cohort. Offspring with prenatal tobacco exposure had an adjusted OR of 1.39 (95% CI, 1.06-1.82) (Table II) compared with unexposed offspring. Further considering the specific exposure level, we observed a stepwise increase in risk per each 5-cigarette daily increase, with an OR of 2.92 (95% CI, 1.20-7.10, *P* for trend = .038) (Table III) for offspring with prenatal tobacco exposure levels of approximately 16 or more cigarettes daily. Post hoc sensitivity analyses including prenatal alcohol intake in the multivariate analyses had, as expected, no effect on the presented estimates (data not shown). In analyses of tobacco exposure during early infancy and at the 11-year follow-up, we observed a moderate crude effect estimate among exposed compared with unexposed (crude OR, 1.58; 95% CI, 1.16-2.15 and crude OR, 1.46; 95% CI, 1.07-1.98, respectively) (Table II), which was attenuated after controlling for prenatal exposure (adjusted OR, 1.17; 95% CI, 0.76-1.79 and adjusted OR, 1.10; 95% CI, 0.77-1.58, respectively) (Table II). In a priori supplementary analyses of prenatal nicotine exposure from NRT, similar effect estimates were observed in the adjusted model, with CIs including null (adjusted OR, 1.36; 95% CI, 0.71-2.59) (Table IV). In post hoc analyses, NRT use in both mothers who quit or continued smoking appeared to additionally increase risk in offspring; however, these analyses were not sufficiently powered and must be interpreted with caution (Table V).

We found no indication that sex modified any of the examined associations. Only for prenatal NRT exposure and maternal psoriasis did the likelihood ratio test suggest a potential effect modification (*P* = .083). In stratified analyses, prenatal NRT exposure was strongly associated with pediatric

Table II. ORs and 95% CIs for risk of psoriasis by prenatal, infantile, and childhood tobacco exposure

Tobacco exposure	Total population, n	Population with psoriasis, n	Models, OR (95%) CI			
			Crude model	Adjusted model 1*	Adjusted model 2†	Adjusted model 3‡
Prenatal						
Total	25 812	281				
No	20 514	201	1 (reference)	1 (reference)	1 (reference)	N/A
Yes	5298	80	1.55 (1.19-2.01)	1.47 (1.12-1.92)	1.39 (1.06-1.82)	N/A
Infantile						
Total	25 812	281				
No	22 687	231	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes	3125	50	1.58 (1.16-2.15)	1.49 (1.09-2.05)	1.42 (1.03-1.94)	1.17 (0.76-1.79)
Childhood						
Total	25 812	281				
No	22 388	230	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes	3424	51	1.46 (1.07-1.98)	1.37 (1.01-1.86)	1.31 (0.96-1.78)	1.10 (0.77-1.58)

CI, Confidence interval; *N/A*, not applicable; *OR*, odds ratio.
*Adjusted for maternal age at birth and highest parental socio-occupational position and prenatal tobacco exposure in all analyses except for prenatal tobacco exposure.
†Additional adjustment for maternal psoriasis status.
‡Additional adjustment for maternal psoriasis status and prenatal tobacco exposure.

Table III. ORs and 95% CIs for increases of 5 cigarettes smoked per day*

Prenatal tobacco exposure cigarettes per day	Total population, n	Population with psoriasis, n	ORs and 95% CIs		
			Crude model	Adjusted model 1†	Adjusted model 2‡
Total	25 522	281			
None	22 825§	235	1 (reference)	1 (reference)	1 (reference)
1-5	936	10	1.04 (0.55-1.96)	0.99 (0.52-1.88)	0.95 (0.50-1.80)
6-10	1167	17	1.42 (0.87-2.33)	1.33 (0.81-2.18)	1.27 (0.77-2.10)
11-15	432	8	1.81 (0.89-3.69)	1.69 (0.82-3.47)	1.55 (0.75-3.20)
≥16	162	5	3.06 (1.25-7.53)	2.96 (1.21-7.26)	2.92 (1.20-7.10)
					P for trend = .038

CI, Confidence interval; *OR*, odds ratio.
*There were 290 observations excluded because of inconsistent/missing data on exposure status.
†Adjusted for maternal age at birth and highest parental socio-occupational position.
‡Additional adjustment for maternal psoriasis status.
§Greater number of observations due to restriction to only current smokers in exposed offspring.

psoriasis only among offspring of mothers with psoriasis (adjusted OR, 4.46; 95% CI, 1.26-15.82; data not shown).

DISCUSSION

We observed an association between prenatal tobacco exposure and pediatric psoriasis, with a monotonic increase in risk per each additional 5 cigarettes smoked daily. Tobacco exposure in early infancy and childhood appeared to be more weakly associated with pediatric psoriasis after controlling for prenatal exposure. Interestingly, the effect estimates for prenatal nicotine exposure from NRT were similar to those of moderate levels of prenatal tobacco exposure; however, these results must be interpreted cautiously.

Although there is considerable evidence that active smoking is an exacerbating or trigger factor in psoriasis,[21] this is, to our knowledge, the first study to use prospectively collected tobacco exposure data to examine its association with pediatric psoriasis. Because our population was drawn from a large prospective birth cohort with repeated longitudinal measures of tobacco exposure, we were able to examine tobacco exposure prenatally, during the first 6 months of life, and at age 11 years, to determine the temporality of our main exposure, despite a lack of data on the specific time point of psoriatic onset. Our findings are therefore of considerable importance in establishing potential risk factors for pediatric psoriasis. Furthermore, using maternal psoriasis status as a proxy for genetic

Table IV. ORs and 95% CIs for prenatal nicotine exposure from nicotine replacements*

Prenatal NRT exposure	Total population, n	Population with psoriasis, n	OR (95% CI)			
			Crude model	Adjusted model 1†	Adjusted model 2‡	Adjusted model 3§
Total	25 805	281				
No	25 277	271	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes	528	10	1.78 (0.94-3.37)	1.75 (0.93-3.30)	1.62 (0.87-3.04)	1.36 (0.71-2.59)

CI, Confidence interval; *NRT,* nicotine replacement therapy; *OR,* odds ratio.
*There were 7 missing observations for exposure.
†Adjusted for maternal age at birth and highest parental socio-occupational position.
‡Additional adjustment for maternal psoriasis status.
§Additional adjustment for maternal psoriasis status and prenatal smoking.

Table V. ORs and 95% CIs for prenatal nicotine exposure by patterns of smoking and nicotine replacement therapy during early pregnancy*

Maternal prenatal NRT and tobacco smoking behaviors	Total population, n	Psoriasis population, n	ORs (95% CI)		
			Crude model	Adjusted model 1†	Adjusted model 2‡
Total	25 805	281			
None	20 420	200	1 (reference)	1 (reference)	1 (reference)
Only NRT	89	§	1.15 (0.16-8.29)	1.15 (0.16-8.34)	0.98 (0.13-7.12)
Quit during pregnancy, not using NRT	2725	40	1.51 (1.07-2.12)	1.41 (0.99-2.00)	1.34 (0.94-1.90)
Quit during pregnancy, using NRT	262	6	2.37 (1.04-5.39)	2.27 (0.99-5.16)	2.10 (0.92-4.81)
Constant smoker, not using NRT	2 132	31	1.49 (1.02-2.18)	1.42 (0.97-2.08)	1.34 (0.92-1.97)
Constant smoker, using NRT	177	§	1.74 (0.55-5.50)	1.71 (0.54-5.40)	1.62 (0.51-5.13)

CI, Confidence interval; *NRT*, nicotine replacement therapy; *OR*, odds ratio.
*There were 7 missing observations for exposure.
†Adjusted for maternal age at birth and highest parental socio-occupational position.
‡Additional adjustment for maternal psoriasis status.
§Clouded because of low number of observations in 1 or more cells.

heritability, we could also examine potential effect modification by genetic predisposition.

Despite these advantages, our study design faced several limitations, the most notable of which was the validity of our maternally reported data on pediatric psoriasis. For approximately half of a subsample of participants in the 11-year follow-up whose mothers reported psoriasis in their child, psoriasis could not be clinically confirmed upon dermatologic examination.[22] It is uncertain in which direction potential misclassification of pediatric psoriasis with atopic dermatitis would bias our results; however, previous findings suggest a weak inverse or null association between prenatal tobacco exposure and atopic dermatitis in the child,[23-25] biasing our results toward null. Residual confounding may also explain our findings. However, our results are both biologically plausible and suggest a risk factor on the mediating pathway between socioeconomic position and pediatric psoriasis—in part, explaining our previously reported strong inverse social gradient in pediatric psoriasis.[26]

We cannot be certain that misclassification of exposure due to underreporting of smoking behavior is not present. Nonetheless, we expect this potential misclassification to be nondifferential for prenatal and infantile exposure. Similarly, selection bias due to cohort attrition and additional restriction to complete cases might have biased our effect estimates. A previous validation study has shown that despite greater attrition rates among participants with lower socioeconomic position in the DNBC, 3 different exposure-outcome associations—including associations between prenatal tobacco exposure and birth weight for gestational age—were not significantly affected by selection bias.[27] Differences in exposure and covariate distribution in our restricted population are likewise not expected to be dependent on outcome, because these data were gathered at baseline, before disease onset; missingness would not likely be influenced by mild psoriatic disease in the child. Sensitivity analyses with all available cases did not differ from complete case analyses (data not shown).

Interpretation

We provide evidence that prenatal tobacco exposure is a risk factor for pediatric psoriasis, especially in those with high levels of exposure. Later exposure in early infancy or childhood may also be associated with pediatric psoriasis; however, our results suggest that the prenatal period is of greatest importance. Given a biologically plausible reason for differential effects by trimester, future studies may be warranted to tease out associations with gestational exposure timing. Later in utero tobacco exposure than we examined could be more or less strongly associated with pediatric psoriasis.

The positive exposure-response relationship we observed for prenatal tobacco exposure indicates a likely biological risk factor. Concentrations of nicotine in fetal serum, placental tissue, and amniotic fluid may exceed the levels observed in serum of the mother, due to ion trapping.[28] This may partially explain the strong associations seen for prenatal tobacco exposure, in which the fetus may be exposed to tobacco metabolites in higher concentrations than when exposed during infancy or childhood[28] because of the more limited exposure duration and nature of the latter 2 periods. Nicotine exposure has been proposed to increase psoriasis risk in adults through interactions with nicotinic acetylcholine receptors, which are present in keratinocytes.[21,29,30] Nicotine may thereby stimulate upward migration of keratinocytes in the epidermal layers in addition to having a strong immune-modulating effect.[21,29,30] Fetal exposure to nicotine appears to lead to metabolic perturbations in the fetus, similar to those observed among active adult smokers.[31] Additionally, fetal immune system development is likely affected by increased amounts of a great number of tobacco metabolites transferred by the mother to the fetus. The aforementioned mechanisms may in part or in whole explain how in utero tobacco exposure increases the risk of pediatric psoriasis.

CONCLUSION

Future studies with similar longitudinal data collection are warranted to corroborate our results; nonetheless, we show that tobacco exposure may be causally associated with psoriasis. Prenatal tobacco exposure is likely a risk factor for pediatric psoriasis.

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