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Atopic dermatitis and tobacco smoke exposure during childhood and adolescence

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Background: Tobacco smoke may affect atopic dermatitis (AD) because of its known effects on humoral and cellular immunity, but prior studies lack data on disease severity and biomarkers over time.

Objective: We investigated the association between passive and active tobacco smoke exposure (TSE) during childhood and adolescence and the activity and severity of AD.

Methods: A birth cohort of 10,521 individuals was followed through adolescence as part of the Avon Longitudinal Study of Parents and Children. We used mixed-effect models to determine the risk of AD (based on repeated assessments) with passive smoke exposure during childhood, active TSE during adolescence, and using a serum biomarker of tobacco exposure (cotinine) at 3 time points.

Results: After adjusting for confounding factors, there was no evidence of a relationship between passive TSE and concurrent AD activity in childhood (adjusted odds ratio, 0.95; 95% confidence interval, 0.83, 1.07) or of an increased risk between active smoking and AD activity in adolescence (adjusted odds ratio, 0.57; 95% confidence interval, 0.44, 0.75). Secondary analyses demonstrated no dose–response relationship and no increased severity of AD with passive or active TSE. Furthermore, we found no increased risk of AD with a cumulative measure of passive TSE across childhood (adjusted relative risk ratio, 0.98; 95% confidence interval, 0.96, 1.00).

Conclusion: Neither active nor passive TSE was associated with AD during childhood and adolescence. (J Allergy Clin Immunol Global 2025;4:100345.)

Key words: *ALSPAC, atopic eczema, atopic dermatitis, epidemiology, tobacco smoke, secondhand smoke*

Abbreviations used

AD:	Atopic dermatitis
ALSPAC:	Avon Longitudinal Study of Parents and Children
aOR:	Adjusted OR
CI:	Confidence interval
FLG:	Filaggrin
OR:	Odds ratio
TSE:	Tobacco smoke exposure

Atopic dermatitis (AD, also known as eczema or atopic eczema) is the most common chronic inflammatory skin disease worldwide, presenting clinically with episodes of intense pruritis and rashes, and conferring a high burden on quality of life.[1,2] The pathophysiology of AD is related to epidermal barrier function and dysregulated immune function.[3] AD characteristically waxes and wanes over time, and environmental factors are postulated to trigger flares, but the particular factors and mechanisms leading to flares of the disease are not adequately understood.[3] Identification of modifiable risk factors is critical for reducing the activity and severity of disease and improving the overall quality of life of patients affected by AD. One common environmental factor that deserves particular attention is tobacco smoke because of its known effects on humoral and cellular immunity.[4,5] Recent estimates report that despite regulations to reduce tobacco smoking, 40% of children worldwide are still exposed to tobacco smoke,[6,7] and that socioeconomically disadvantaged children are most affected.[7-9]

Studies that have examined tobacco smoke exposure (TSE) as a risk factor for AD report conflicting results. A recent systematic review and meta-analysis of 86 studies found that overall, active smoking (ie, someone who currently smokes) was associated with an 87% increased odds of AD (odds ratio [OR], 1.87; 95% confidence interval [CI], 1.32, 2.63) and passive smoking (ie, someone exposed to secondhand smoke) was associated with an 18% increase (OR, 1.18; 95% CI, 1.01, 1.38); however, most studies had methodologic limitations, and there was a high level of heterogeneity in the results.[10] The majority of studies were cross-sectional. Only 11 studies addressed the level of passive TSE, and only 2 addressed the level of active smoking. Only one study addressed AD severity, and no studies examined the relationship between AD severity and active smoking.[10] Very few studies collected objective measures of smoke exposure (eg, using a biological marker such as blood or urine cotinine). Finally, there was substantial variability in the extent to which studies controlled for other potential confounding factors, such as socioeconomic status, which are known to be independently associated with both TSE and AD.[10,11] Additionally, other studies did not account for gene–environment interactions, most notably the interaction between TSE and filaggrin *(FLG)* gene loss-of-function mutations, which disrupt skin barrier formation and have been shown to have interactions with some environmental

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factors, such as cat ownership, water hardness, and phthalate exposure.[12] Given the many limitations of prior studies, additional research on the role of TSE on AD is needed. Our objective was to determine the extent to which TSE during childhood and active smoking during adolescence affects AD activity and severity over time.

METHODS

Data

The Avon Longitudinal Study of Parent and Children (ALSPAC) is a birth cohort study based at the University of Bristol in the United Kingdom designed to study the effect of genetic, biological, psychological, social, and environmental exposures on health and development.[13,14] In 1991 and 1992, a total of 14,541 pregnant women in the United Kingdom were recruited to the study, and for over 25 years, the study has been following these women, their partners, and their children. Of these initial pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. The study population is largely representative of the UK population as a whole. The study's website contains details of all the information available through a fully searchable data dictionary and a variable search tool.[15]

Exposure

TSE was based on maternal self-report of passive exposure at 6 time points during childhood (age 2, 3, 4, 5, 6, and 8 years), self-reported active smoking at 4 time points during adolescence (age 10, 13, 15, and 17 years), and serum cotinine levels at ages 6, 15, and 17 years (Fig 1). Cotinine is the primary metabolite of nicotine and, with a biological half-life of 15 to 20 hours, it is the preferred serum biomarker for TSE.[16,17] Mothers reported the average number of hours of passive TSE on weekdays and weekends, and the combination was used (see Fig E1 in the Online Repository available at www.jaci-global.org) to classify a child's TSE as none; low, indicating up to 3 hours a day on average; or high, indicating >3 hours a day on average. To assess cumulative TSE, at each time point, children were assigned 0 points for no TSE, 1 point for low TSE, and 2 points for high TSE; point totals were then summed across the 6 time points in childhood. For adolescents, active smoking was classified as none, low (less than once a week), or high (at least once a week) (see Fig E2 in the Online Repository).

Outcome

The primary outcome was AD disease activity, a single outcome measured repeatedly at 10 time points through a standardized question[13] about flexural dermatitis between ages 6 months and 18 years: "Have you (or your child) had an itchy, dry skin rash in the joints and creases of the body (eg, behind the knees, elbows, under the arms) in the past year?" Mothers answered this question for their children up to age 13, and teens answered at ages 16 and 18. Individuals were considered to have active AD if they had at least 2 reports of flexural dermatitis, up to and including the time point being considered.[13,14] At the first report of flexural dermatitis, cases were categorized as being indeterminate for AD and were not included in the healthy control group for that time point. Disease severity was assessed at each time point by a question asking mothers to categorize their child's disease over the last year as "no problem," "mild," "quite bad," or "very bad." For our analyses, we grouped "no problem" and "mild" AD in a "no problem/mild" category, and "quite bad" and "very bad" AD in a "moderate/severe" category. Finally, children were classified as having inactive AD if they met the definition of active AD previously but did not report an itchy rash during the year before the time point being considered.

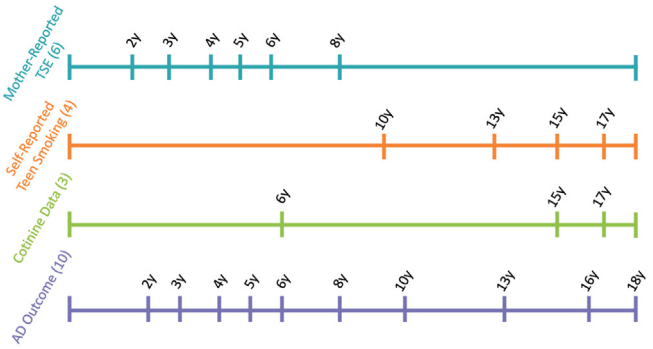

FIG 1. Exposure and outcome data time points. Mother-reported data on TSE were collected at 6 time points throughout childhood. Self-reported data on teen smoking were collected at 4 time points throughout adolescence. Serum cotinine levels were measured at 3 time points, and outcome data on AD were collected at 10 time points.

Covariates

On the basis of prior literature, several potential confounders were accounted for in the adjusted analyses including sex, ethnicity, and socioeconomic status (see Fig E3 in the Online Repository available at www.jaci-global.org).[8,10,18-20] Because prior literature indicated that socioeconomic status was considered to be a strong confounder, we included multiple measures covering various aspects of this domain: maternal and paternal educational level, social class based on occupation (highest level of either parent at either 18 or 32 weeks' gestation), a financial difficulties quartile (categorized according to mother's self-reported difficulty to afford food, clothing, heating, rent or mortgage, and items necessary to care for her child), household crowding index (number of persons per room per household), housing tenure (owned, privately rented, or rented from a council or housing association), neighborhood quality index (objective measure), and neighborhood quality rating and stress score (mother's self-reported concern about potential neighborhood and/or household problems, including ventilation, noise levels, litter, vandalism, and burglary).

Analysis

We first provided descriptive statistics of the cohort, then determined the prevalence of parent- and self-reported smoking data across childhood and adolescence. We then compared self-reported smoking to the distribution of serum cotinine levels at available time points.

We performed cross-sectional multivariable regression analyses at each time point to determine the odds of active AD among individuals with any passive TSE across 6 time points and any active smoking across 4 time points. For longitudinal analyses, we used mixed-effect models to determine the average

subject-specific OR across all time points for passive and active TSE. In secondary analyses, we repeated the models to determine the odds of having any AD by TSE level (none, low, or high) and then the relative risk ratio of having higher severity AD (none, no problem/mild AD, or moderate/severe AD) by any TSE. We also performed a sensitivity analysis using serum cotinine level to address possible ascertainment bias in exposure.

Finally, because poor skin barrier function could make individuals more susceptible to the effect of TSE, we evaluated for possible effect modification by filaggrin mutation status. In the analysis, filaggrin status was coded as a binary variable, either with the wild-type *FLG* gene responsible for skin barrier function, or having at least one loss-of-function null mutation in either the R501X or 2282del4 sequence within the *FLG* gene.[12,21,22]

The adjusted models included all the covariates listed above. Asthma and allergic rhinitis were not included as covariates in the adjusted model because they were considered colliders in the association between TSE and AD—that is, it is more likely to be causally influenced by the exposure and outcome than vice versa; TSE has been associated with the development and exacerbation of asthma and allergic rhinitis in children, and although not all patients have disease that follows the atopic march, AD is often diagnosed first and may lead to asthma and allergies (Fig E3). Nonetheless, because participants with asthma and rhinitis may avoid TSE, and because the association between AD and other atopic disease may be bidirectional, we also performed sensitivity analyses including allergic rhinitis, asthma, and both as potential confounders in the models. To account for intermittent missing data and attrition (ie, loss to follow-up) in the ALSPAC cohort, we used a flexible modeling strategy that accounted for missing outcome data; our prior work suggests that multiple imputation of missing exposure and covariate data are unlikely to affect our results.[23] All statistical analyses were performed by Stata v14.2 software (StataCorp, College Station, Tex).

Ethical approval for the study was obtained from the ALSPAC ethics and law committee and the local research ethics committees. Consent for biological samples was collected in accordance with the 2004 Human Tissue Act. Informed consent for the use of data collected by questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC ethics and law committee at the time. The study was considered exempt from University of California, San Francisco, institutional review board review because all data obtained by investigators were fully deidentified.

RESULTS

Cohort characteristics

There were 10,521 children in the ALSPAC cohort who were alive at 1 year and who had at least one report of their AD status (Table I). Compared to children who never developed AD, children with AD (13-21% at each time point) were more likely to be female, to have ever had asthma by the age of 18, to have ever had allergic rhinitis by the age of 18, and to have a loss-of-function mutation in the *FLG* gene (either 2282del4 or R501X). Children with AD also had unique socioeconomic characteristics compared to children without AD: they were more likely to have a mother with a university degree (16% vs 11%), to have a father with a university degree (22% vs 16%), to be from a professional social class (14% vs 10%), to have a household crowding index of ≤0.5 (47% vs 40%), and to have parents who owned or mortgaged (rather than rented) their home during pregnancy (81% vs 73%).

Exposure and outcome data

The proportion of children who experienced some (>0 hours a day) mother-reported TSE at each time point ranged from 25% to 42% (Tables II and III). At 3 years of age, the percentage of children with high TSE peaked at 12% and decreased progressively with age. The number of teens who reported actively smoking increased progressively with age. By 18 years old, 28% of adolescents smoked at least once in the previous month, including 17% who smoked at least once a week.

Higher levels of mother-reported TSE and higher levels of teen-reported active smoking were both associated with higher serum cotinine levels, although there were outliers in each group (see Fig E4 and Table E1 in the Online Repository available at www.jaci-global.org).

The percentage of children in the cohort who had active AD ranged from 13% to 21% between the ages of 2 and 18 years old (see Table E2 in the Online Repository available at www.jaci-global.org). Across all time points, the majority (51-68%) of individuals with AD reported mild severity.

Passive TSE findings

While there was an inverse association between any passive TSE and any concurrent AD at most time points in the unadjusted analyses, all these inverse associations became insignificant after adjusting for confounding factors (see Table E5, *A,* in the Online Repository available at www.jaci-global.org). In the adjusted model, there was no significant association between having any AD and any passive TSE in childhood (adjusted OR [aOR] longitudinally across childhood, 0.95; 95% CI, 0.83, 1.07; Table IV). In the adjusted models, there was no significant association between having AD and having a high level of passive TSE compared to no passive TSE (Table IV; Table E5, *B*), and there was no significant association between having severe AD and having any passive TSE (Table IV; Table E5, *C*). Finally, after adjusting for confounding, there was no increased risk of AD with increased cumulative TSE across childhood (adjusted relative risk ratio, 0.98; 95% CI, 0.96, 1.00).

Active TSE findings

In the active smoking models, 1 of 4 time points demonstrated an inverse association between active smoking status and active AD, which remained in the adjusted longitudinal model (aOR, 0.57; 95% CI, 0.44, 0.75; Table E5, *A*). However, we did not see dose–response in secondary analyses; there was no change in adjusted odds of having any AD with a high level of active TSE, although there was a decreased adjusted odds of AD with a low level of active TSE (aOR, 0.69; 95% CI, 0.49, 0.97; Table IV; Table E5, *B*). Finally, active TSE was associated with a decreased adjusted risk of no problem or mild AD compared to having no AD (adjusted relative risk ratio, 0.48; 95% CI, 0.36, 0.97; Table IV; Table E5, *C*). However, this association was not present in association with moderate/severe AD.

TABLE I. Cohort descriptive data

Characteristic	Total*	Overall	AD	
			Never (n = 5,516; 52%)	Ever (n = 5,005; 48%)
Child sex (male)	12,095	6,252 (52)	2,992 (54)	2,399 (48)
Child ethnicity (White)	11,149	10,645 (95)	4,718 (95)	4,550 (96)
Child asthma ever†	12,087	3,229 (27)	1,046 (19)	1,805 (36)
Child allergic rhinitis ever‡	12,099	1,376 (11)	329 (6)	926 (19)
FLG gene loss-of-function mutation (2282del4 or R501X)	8,891	769 (9)	220 (6)	478 (12)
Maternal highest education§				
CSE/none	11,415	2,111 (18)	1,098 (22)	737 (15)
Vocational	11,415	1,101 (10)	506 (10)	452 (9)
O level	11,415	4,022 (35)	1,822 (36)	1,672 (35)
A level	11,415	2,644 (23)	1,115 (22)	1,201 (25)
Degree	11,415	1,537 (13)	555 (11)	772 (16)
Paternal highest education§				
CSE/none	11,002	2,704 (25)	1,354 (28)	981 (21)
Vocational degree	11,002	925 (8)	424 (9)	377 (8)
O level	11,002	2,378 (22)	1,067 (22)	1,013 (22)
A level	11,002	2,922 (27)	1,270 (26)	1,287 (27)
University degree	11,002	2,073 (19)	766 (16)	1,030 (22)
Social class¶				
Unskilled	11,532	83 (1)	42 (1)	27 (1)
Partly skilled	11,532	427 (4)	214 (4)	149 (3)
Skilled manual	11,532	1,432 (12)	696 (13)	533 (11)
Skilled nonmanual	11,532	3,107 (27)	1,483 (29)	1,225 (25)
Managerial and technical	11,532	5,092 (44)	2,228 (43)	2,239 (46)
Professional	11,532	1,391 (12)	524 (10)	681 (14)
Financial difficulties quartile‖				
Lowest	11,476	4,446 (39)	1,950 (38)	1,961 (40)
Mild	11,476	1,541 (13)	700 (14)	615 (13)
Moderate	11,476	3,353 (29)	1,505 (29)	1,416 (29)
Highest	11,476	2,136 (19)	973 (19)	862 (18)
Household crowding index#				
≤0.5	11,421	4,942 (43)	2,039 (40)	2,260 (47)
>0.5-0.75	11,421	3,601 (32)	1,614 (32)	1,524 (15)
>0.75-1	11,421	2,212 (19)	1,096 (21)	827 (17)
>1	11,421	666 (6)	368 (7)	209 (4)
Home ownership status				
Owned or mortgaged	11,586	8,857 (76)	3,821 (73)	3,917 (81)
Rented (private landlord)	11,586	771 (7)	377 (7)	282 (6)
Rented (from council or housing association)	11,586	1,602 (14)	837 (16)	535 (11)
Other	11,586	356 (3)	183 (4)	127 (3)
Neighborhood rating by mother				
Very/fairly good area	11,415	10,593 (93)	4,758 (92)	4,475 (93)
Bad/not very good area	11,415	822 (7)	390 (8)	317 (7)
Neighborhood quality index**				
Very low quality	11,738	3,001 (26)	1,430 (27)	1,186 (24)
Low quality	11,738	2,740 (23)	1,222 (23)	1,154 (23)
High quality	11,738	4,751 (40)	2,097 (40)	2,047 (42)
Very high quality	11,738	1,246 (11)	544 (10)	534 (11)
Neighborhood stress classification††				
Very low	10,290	2,834 (28)	1,271 (29)	1,209 (26)
Low	10,290	2,950 (29)	1,256 (28)	1,322 (29)
High	10,290	2,567 (25)	1,081 (24)	1,170 (26)
Very high	10,290	1,939 (19)	807 (18)	874 (19)

Data are presented as nos. (%).

*Total includes individuals who may have had AD (ie, single episode with no subsequent confirmatory episode).

†Child ever had asthma by age 18 years.

‡Child ever had allergic rhinitis by age 18 years.

§*CSE* indicates Certificate of Secondary Education (conferred certificate considered equivalent to O levels); *O level,* ordinary levels (represents 11 total years of study, marking end of secondary education cycle); and A level, advanced levels (represents 13 total years of study, considered preuniversity qualification).

¶Determined based on highest occupational level from either parent as classified by National Statistics Socio-economic Classification.

‖Numeric score of how difficult mother finds it to afford key items (food, clothing, heating, rent/mortgage, things for baby), sorted by quartile.

#Numeric value calculated by dividing number of people in household by number of rooms in house, ranging from 0 to >1.

**Classified based on mother's report on whether neighborhood is lively, friendly, noisy, clean, attractive, and polluted or dirty.

††Classification based on mother's report of child's home having following qualities: badly fitted doors and windows, poor ventilation, noise (from other rooms of home, other homes, or street), rubbish/litter dumped around neighborhood, dog dirt on pavement, disturbance from teenagers or youths, and worry about vandalism, burglaries, muggings, or attacks.

TABLE II. Mother-reported smoking prevalence in their children

Child age (years)	Mother-reported TSE			Child serum cotinine (ng/mL),* median (IQR)
	None (0 h/d)	Low (≤3 h/d)	High (>3 h/d)	
2	6151 (60%)	2941 (29%)	1080 (11%)	—
3	5327 (58%)	2786 (30%)	1147 (12%)	—
4	5856 (61%)	2934 (30%)	860 (9%)	—
5	5564 (63%)	2669 (30%)	554 (6%)	—
6	5611 (67%)	2400 (29%)	381 (5%)	1.09 (0.59, 1.61)
8	6109 (75%)	1791 (22%)	262 (3%)	—

Serum cotinine was only measured at ages 6, 15, and 17 years.
IQR, Interquartile range.

TABLE III. Teen-reported smoking prevalence

Teen age (years)	Teen-reported active smoking			Teen serum cotinine (ng/mL), median (IQR)
	None	Less than once a week	At least once a week	
10	7266 (98%)	85 (1%)	8 (0)	—
13	5524 (91%)	438 (7%)	138 (2%)	—
15	4420 (82%)	384 (7%)	555 (10%)	0.86 (0.26, 1.37)
17	3016 (72%)	464 (11%)	716 (17%)	1.06 (0.75, 12.89)

Serum cotinine was only measured at ages 6, 15, and 17 years.
IQR, Interquartile range.

TABLE IV. Mixed effects logistic regression analysis of AD by TSE

Analysis	Reference	Variable	Point estimate (95% CI) for:	
			Passive TSE	Active TSE
Primary analysis: Any TSE exposure and any AD	None	—	aOR: 0.95 (0.83, 1.07)	aOR: 0.57* (0.44, 0.75)
Secondary analysis 1: By TSE severity	None	Low TSE	aOR: 0.95 (0.84, 1.08)	aOR: 0.69* (0.49, 0.97)
		High TSE	aOR: 0.80 (0.62, 1.04)	aOR: 0.69 (0.45, 1.05)
Secondary analysis 2: By AD severity	None	No problem/mild AD	aRRR: 0.93 (0.82, 1.05)	aRRR: 0.48* (0.36, 0.64)
		Moderate/severe AD	aRRR: 1.06 (0.87, 1.28)	aRRR: 1.04 (0.72, 1.50)

Full adjusted regression results are provided in Table E4. Cross-sectional and unadjusted regression results are provided in Table E5.
aRRR, Adjusted relative risk ratio.
*$P < .05$. Adjusted analyses include the following covariates: sex, ethnicity, maternal and paternal highest educational level, social class based on occupation, financial difficulties score, housing tenure, household crowding index, neighborhood rating by mother, neighborhood quality index, neighborhood stress, and filaggrin.

Sensitivity analyses

Serum cotinine levels and AD. Serum cotinine analyses demonstrated that there was no association between a 1-unit natural logarithmic increase in child serum cotinine level and the odds of AD either in the unadjusted and adjusted models at age 6, 15, or 17 (Fig 2). Measured child serum cotinine level was analyzed by AD severity level, and we consistently found no meaningful difference in serum cotinine level distribution for each AD severity category at age 6, 15, or 17 (see Fig E5 in the Online Repository available at www.jaci-global.org).

Asthma and allergic rhinitis. Asthma and allergic rhinitis were not included as covariates in the primary model because they are considered potential colliders (ie, causally influenced by both exposure and outcome) in the association between TSE and AD. However, sensitivity analyses were performed, and adding allergic rhinitis, asthma, or both as covariates in the model did not lead to qualitatively different findings (see Table E6 in the Online Repository available at www.jaci-global.org).

Gene–environment interaction

In all passive and active longitudinal models, the interaction term between TSE and filaggrin mutation did not show evidence of a gene–environment interaction (OR, 0.42-5.48; $P > .05$).

DISCUSSION

In a longitudinal birth cohort followed for nearly 2 decades with repeated measures of both passive TSE and active smoking, we did not find an increased risk of AD activity or severity with either passive or active TSE. Results from a limited set of time points with an objective biomarker of smoke exposure confirmed our results and there was no evidence of a gene–environment interaction by *FLG* mutation status.

Our findings are at odds with a 2016 meta-analysis that found that active smoking was associated with an 87% increased risk of AD (OR, 1.87; 95% CI, 1.32, 2.63) and that passive TSE was associated with an 18% increase in risk of AD (OR, 1.18; 95% CI, 1.01, 2.38).[10] It is worth noting that in this meta-analysis, the largest studies and those with the highest study quality ratings had findings concordant with ours: they also did not show an association between TSE and AD. Our study was more robust in that it included longitudinal data across numerous time points, secondary analyses to stratify by level of TSE, data on AD severity, and sensitivity analyses with objective serum cotinine levels, which further support our primary findings.

Our results also suggest an important role for confounding by socioeconomic status, which may have been inadequately controlled for in other studies. Many of our unadjusted regression models showed an inverse relationship between TSE and AD

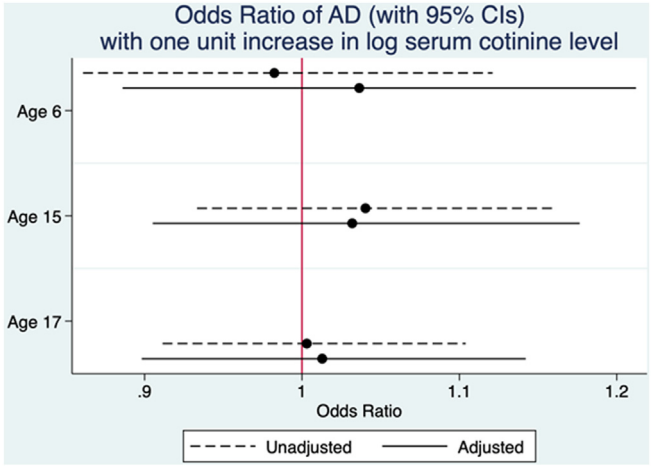

FIG 2. Odds ratio of AD with 1-unit increase in log serum cotinine level. Odds of AD (with 95% CIs) with a 1-unit increase in log serum cotinine level at ages 6, 15, and 17. Adjusted analyses include: sex, ethnicity, maternal and paternal highest educational level, social class based on occupation, financial difficulties score, housing tenure, household crowding index, neighborhood rating by mother, neighborhood quality index, and neighborhood stress.

(ie, higher mother-reported TSE was associated with a lower relative risk of AD). However, once the confounding variables were controlled for in the adjusted models, we observed no association.

In the active smoking primary analysis, there was an inverse association between TSE and AD in the fully adjusted model (Table IV), potentially due to residual unmeasured confounding; however, this association is less likely to be meaningful given that the secondary analyses failed to show a dose–response relationship across smoking levels or a consistent inverse association when stratified by AD severity. Interestingly, fewer participants fell into the high-exposure category, which may possibly relate to the lack of a clear dose response.

In all adjusted models, filaggrin mutation was a significant covariate; however, after testing the interaction between filaggrin status and either passive TSE or active smoking, all terms had $P > .05$, suggesting that there is no effect modification by filaggrin. This finding is consistent with the conclusions of a previous meta-analysis evaluating AD etiology and *FLG* gene–environment interactions, which included potential interactions with maternal smoking during pregnancy as well as childhood environmental TSE.[12] Notably, only 9% of the genotyped sample had one of the two *FLG* gene mutations in the study (2282del4 or R501X), so the sample may be underpowered to detect a gene–environment interaction. Furthermore, there are additional, less prevent filaggrin null mutations that were not accounted for in this study.

It is important to note the several limitations of our study. As has been described in detail elsewhere, there are both intermittent missing data and attrition (ie, loss to follow-up) in the ALSPAC cohort.[23] We used a flexible modeling strategy that accounted for missing outcome data, and our prior work suggests that multiple imputation of missing exposure and covariate data are unlikely to affect the results.[23] Overall, serum cotinine levels reinforced the validity of mother-reported and self-reported smoking data, but there was some evidence of reporting bias because some adolescents who reported not smoking had serum cotinine levels well above the standardized cutoff of 3 ng/mL for active smoking established by National Health and Nutrition Examination Survey (aka NHANES) (Table E1); similarly, some children with no mother-reported TSE had serum cotinine levels well above the expected range (Fig E4), which could either be due to reporting bias or TSE from sources unknown to the mother. Another limitation of our study is that our definition of AD is based on parental report. Reassuringly, prior studies have found that parental report closely approximates physician assessment of AD,[24] and the estimates of the annual period prevalence of AD were consistent with UK estimates from the population-based International Study of Asthma and Allergies in Childhood (aka ISAAC) studies that included physical assessment in childhood.[25] Finally, the ALSPAC cohort is predominantly white, and more diverse cohorts should be studied to ensure our results' generalizability.

Finally, although we did not observe a meaningful association between passive or active TSE and AD, it is critical to reiterate the other innumerable adverse health effects associated with TSE, especially among developing children and adolescents. Our results suggest that tobacco smoke is not an important driver of AD in a large UK birth cohort. Furthermore, our findings highlight the importance of adjusting for socioeconomic status and accounting for both the level of TSE and the activity and severity of AD in longitudinal analyses.

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