

Environmental and dietary risk factors for infantile atopic eczema among a Slovak birth cohort

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Infantile atopic eczema (AE) is a risk marker for future asthma. This study assesses the contribution of modifiable exposures to infantile AE. If modifiable exposures contribute substantially to infantile AE, its prevention might be a sensible approach to asthma prevention. Pregnant women ($n = 1978$) were systematically recruited from maternity hospitals of the Slovak Republic; their birthed cohort of 1990 children were prospectively followed for 1 yr. Children's exposures to selected environmental and dietary factors were assessed via maternal questionnaires administered at delivery and 1 yr of age. A child was considered to have AE, based on physical examination (SCORAD index > 2) or mother's report of a previous physician diagnosis. Multivariate logistic regression was used to calculate adjusted odds ratios and percent total regression scores (TRS) for each variable. At 1 yr of age 1326 (67%) of the children remained in the cohort and 207 (15.6%) developed AE. Various modifiable environmental and dietary exposures increased the likelihood of AE (ownership of cats; consumption of infant formula, eggs, and fish) while others decreased the likelihood of AE (ownership of livestock; exclusive breast feeding for ≥ 4 months). Overall, modifiable exposures contributed less to the TRS than did non-modifiable exposures (38% vs. 62%, respectively). The modifiable exposure category that contributed most to the TRS was infant feeding practices (27.5% TRS). Modifiable exposures – especially those related to infant feeding practices – significantly contribute to infantile AE, although modifiable factors contribute less overall than do non-modifiable exposures.

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Studies from diverse industrialized regions of the world reveal an increasing prevalence of all clinical manifestations of allergic disease (1–9), including atopic eczema (AE) (4, 10–15), asthma (7, 16–18), hay fever (19, 20), and reactions to foods, drugs, and insects (6). AE is one of the earliest clinical manifestations of allergic disease (21), with the highest incidence occurring during the first 3 months of life (22–24).

Infantile AE (that develops prior to 1 yr of age) is a risk marker for the later development

of asthma and is associated with sensitization to respiratory allergens and wheezing (25–29). Prospective cohort studies estimate that those with infantile AE have a two- to ninefold increased risk of developing asthma (25, 30). The association between maternal smoking and asthma is stronger among children with early AE (31).

If modifiable risk factors that contribute substantially to the development of infantile AE can be identified and exposures limited, the

prevention of AE might be a sensible approach to asthma prevention (32, 33). If modifiable risk factors are not found to be important contributors to infantile AE, efforts to prevent asthma might better target those children affected with AE.

Non-modifiable risk factors for infantile AE include parental history of atopy (34–37), male gender (38–40), low birth order (41, 42), season and month of birth (29, 43), and a complicated pregnancy or perinatal course (44, 45). Retrospective studies link low birth weight (46) and prematurity (47) to infantile AE.

Modifiable risk factors for infantile AE might include environmental and dietary exposures, however, the literature regarding many of these modifiable factors is contradictory. This study seeks to quantify the contribution of various modifiable environmental and dietary exposures to the development of infantile AE. This information may be useful in determining sensible prevention strategies for the prevention of infantile AE and possibly asthma.

Methods

Study design

This prospective cohort study assesses the contribution of modifiable environmental and dietary exposures to the development of infantile AE. This study was approved by the Institutional Review Boards of the Institute of Preventive and Clinical Medicine, Slovak Republic, and the Centers for Disease Control and Prevention, USA. All procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki of 1975, revised in 1983.

Participants

Between January 1, 1997 and August 31, 1999, the first 250 pregnant women delivering at maternity hospitals in the selected study sites were recruited if they met the following criteria: (i) residence within the catchment area of the hospital during pregnancy and no immediate plans to move to another region; (ii) non-Romanic ethnicity; (iii) delivery of a full-term infant. A total of 1978 (98.9%) of the 2000 women provided informed consent to enroll in the study and their birthed cohort of 1990 children were followed prospectively. After 12 months, 1326 (67%) of the children remained in the cohort, and they received clinical examination and their mothers were interviewed.

Setting

The eight selected study sites (Levice, Nove Zamky, Kosice, Snina, Spiska-Nova Ves, Ruzomberok, Bratislava, and Michalovce) were chosen based on the possibility of co-operation with the regional maternity hospitals and the nature of the region, defined as follows: rural region types are those with minimal farming and use of chemical fertilizers; agricultural region types are those with extensive farming and wide use of chemical fertilizers; and industrial region types are those with a large number of industrial plants producing or processing chemicals, power, textiles or metals.

Data collection

Questionnaire data. Two questionnaires were administered: the first by the attending obstetricians to the mothers of the birthed cohort during their delivery admission, and the second by the allergists at a clinical evaluation of the infants at 1 yr of age. Both questionnaires elicited demographic, education, health, and household characteristics, as well as pregnancy, perinatal, environmental, and dietary history.

A parental history of atopy was any reported history of asthma, AE or hay fever for either parent. High parental education was reported completion of secondary school with A-levels or higher. A high-risk pregnancy was one complicated by infection, bleeding, anemia, hypertension, pre-eclampsia/eclampsia or pre-term labor. Low birth weight was defined as <2500 g. Residence near heavy traffic was defined as living <100 m from a road with >20 automobiles per hour. Other furred house pets included dogs, hamsters, guinea pigs, and rabbits. Livestock included horses, cows, goats or sheep.

Clinical data. At 1 yr of age, the birth cohort underwent a standardized clinical evaluation consisting of a questionnaire completed by the mother and physical examination of the child. Physical examinations were performed by allergists who underwent training in the assessment of AE based on the SCORAD index (48, 49). A case of AE represented a child whose physical examination yielded a SCORAD index >2 or whose mother reported a physician diagnosis of AE.

Data analyses

For purposes of this study, 'modifiable' exposures were considered to be those exposures that an individual can readily control such as diet and

individual health behaviors, including cigarette smoking. 'Non-modifiable' were considered to be those exposures over which an individual may have little or no control or circumstances that an individual may not readily change, including parental history of atopy, gender, birth order, pregnancy, and perinatal circumstances, timing of birth, geographic residence, and parental education.

For univariate analyses, 2×2 contingency tables were constructed for each exposure variable and AE, and a Mantel-Haenszel chi-square statistic (with associated p-value) was calculated. Multivariate modeling was performed first by using a model containing all exposure variables (as main effects) and all interaction terms, with the subsequent elimination of all interaction terms as none were found to be significant using a likelihood ratio test. Collinearity among all exposure variables was assessed using 'collin.mac,' a SAS collinearity macro developed by the Rollins School of Public Health of Emory University (Atlanta, GA, USA); no significant collinearity was found, thus, all exposure variables were retained in the final logistic model. A Hosmer-Lemeshow goodness-of-fit statistic was calculated for the final logistic model to assess how the model fit the data.

For each exposure variable in the final logistic model, an adjusted odds ratio (OR_{adj}), 95% Wald's CI, and percent total regression score (TRS), which reflects the percent of total variance explained by the model that is attributable to a particular variable, were calculated. The percent TRS was calculated by dividing the chi-square score statistic for each particular variable by the chi-square score statistic for the full model. All analyses were performed with SAS statistical software, version 8.02 for Windows (SAS Institute Inc., Cary, NC, USA) between January and June 2003. Statistical significance was set at $\alpha = 0.05$, two-tailed, for all analyses.

Results

Prevalence of AE

Of the 1326 Slovak children recruited and followed in this study, 207 (15.6%) had AE by 1 yr of age [101 (48.8%) had a SCORAD index > 2 and 106 (51.2%) had a mother's report of a physician diagnosis of AE].

Univariate analyses

The prevalence of many non-modifiable exposures was significantly different (either greater or lesser)

between children with and without AE (Table 1). Children with AE were more likely to have mothers or fathers with atopy ($p < 0.05$), to have a father with a higher education level ($p < 0.05$), to not have had a low birth weight ($p < 0.05$), to be born in the winter ($p < 0.05$) but not in the spring ($p < 0.0001$), to reside in a rural ($p < 0.01$) but not in an agricultural ($p < 0.001$) region, and to reside in a town vs. a village ($p < 0.05$) compared with children without AE.

The prevalence of many modifiable exposures was also significantly different (either greater or lesser) between children with and without AE (Table 1). Children with AE were less likely to have parents who owned livestock ($p < 0.05$), more likely to have been fed any formula ($p < 0.05$) or cow's milk ($p < 0.05$), and less likely to have been exclusively breast fed for ≥ 4 months ($p < 0.01$).

Multivariate analyses

The logistic model fit well ($p = 0.9623$ for Hosmer-Lemeshow goodness-of-fit statistic). Among non-modifiable exposures, those children with AE were 1.5 times as likely to have a mother with atopy (95% CI = 1.1–2.2) and 1.64 times as likely to have a father with atopy (95% CI = 1.1–2.6) (Table 2). Those children with AE were 1.27 times as likely to have a father with high educational status (95% CI = 1.04–1.5), 1.59 times as likely to reside in a town vs. a village (95% CI = 1.05–2.4), 0.48 times as likely to be born in the spring (95% CI = 0.3–0.7), and 0.46 times as likely to reside in an agricultural region (95% CI = 0.3–0.8).

Among modifiable exposures, those children with AE were 1.36 times as likely to have a parent who smoke tobacco (95% CI = 1.01–1.8), 1.60, 1.92, and 1.56 times as likely to have dietary exposure to formula, eggs, and fish, respectively. Children with AE were 0.66 times as likely to have central heat in their homes and 0.30 times as likely to be exclusively breast fed for ≥ 4 months.

For the birth cohort considered as a whole, modifiable factors accounted for 38.2% of the TRS (Table 2; Fig. 1). The exposure category that accounted for the greatest percentage of the TRS was infant feeding practices (27.5% TRS), with breast feeding for ≥ 4 months contributing more than any other dietary exposure (6.4% TRS). However, the single exposures accounting for the greatest percentage of the TRS were non-modifiable in nature: birth in the spring (11.7%), high paternal education (9.7%), and residence in an agricultural region (9.3%).

Table 1. Prevalence of non-modifiable and modifiable exposures among Slovak children, by infantile atopic eczema (AE) status

Exposure	AE + (n = 207)	AE – (n = 1119)	p-value
<i>Non-modifiable factors</i>			
Family history of atopy			
Maternal history	45 (21.7)	174 (15.6)	0.03*
Paternal history	35 (16.9)	120 (10.7)	0.01*
Parental education			
High maternal education	141 (68.1)	727 (65)	0.38
High paternal education	129 (62.3)	608 (54.8)	0.03*
Pregnancy- and fetal-related factors			
Maternal age ≥ 35 yr	14 (6.8)	48 (4.3)	0.12
High-risk pregnancy	45 (21.7)	190 (17)	0.09
Antibiotics used in the pregnancy	40 (19.3)	197 (17.6)	0.55
Male gender	116 (56)	544 (48.5)	0.05
Birth order higher than one	90 (43.5)	508 (45.6)	0.61
Low birth weight infant	3 (1.5)	52 (4.7)	0.03*
Winter birth	73 (35.3)	314 (28.1)	0.03*
Spring birth	51 (24.8)	433 (38.7)	0.0001*
Summer birth	58 (28.2)	271 (24.2)	0.23
Autumn birth	24 (11.6)	101 (9)	0.24
Region type			
Rural	37 (17.9)	126 (11.3)	0.0078*
Agricultural	39 (18.8)	351 (31.4)	0.0003*
Industrial	131 (63.3)	635 (56.8)	0.08
Residential factors			
Residence near heavy traffic	114 (55.6)	575 (52.5)	0.41
Residence in town vs. village	149 (72)	708 (63.3)	0.016*
Residence in house vs. flat	91 (44)	494 (44.2)	0.96
<i>Modifiable factors</i>			
Fuel type for heating and cooking			
Central heat	115 (55.6)	649 (58)	0.51
Electricity	49 (23.7)	302 (27)	0.32
Coal stove	15 (7.3)	64 (5.7)	0.39
Wood fuel	15 (7.3)	78 (7)	0.88
Gas	154 (74.4)	772 (69)	0.12
Parental smoking			
Mother smokes	7 (3.4)	54 (4.8)	0.36
Father smokes	82 (39.6)	505 (45.1)	0.14
Either parent smokes	83 (40.1)	515 (46.1)	0.12
Other household exposures			
Mold or cockroach problems in the home	11 (5.3)	64 (5.7)	0.82
Carpeting or featherbed in the home	203 (98.1)	1091 (97.5)	0.81
Animal ownership			
Own cat	40 (19.3)	177 (15.8)	0.21
Own other furred housepet	83 (40.1)	444 (39.7)	0.91
Own bird	11 (5.3)	40 (3.8)	0.23
Own livestock	33 (15.9)	246 (22)	0.04*
Infant feeding			
Any formula in the first year of life	178 (86.8)	892 (79.9)	0.02*
Exclusive breast feeding for ≥ 4 months	5 (2.4)	86 (7.7)	0.006*
Introduction of solid food < 4 months	103 (49.8)	632 (56.5)	0.07
Cow's milk in the first year of life	184 (90.2)	941 (84.6)	0.04*
Eggs in the first year of life	179 (88.2)	1028 (92.1)	0.06
Citrus fruit in the first year of life	175 (85.8)	991 (88.8)	0.22
Fish in the first year of life	158 (77.5)	923 (82.8)	0.07
Nuts in the first year of life	50 (24.8)	285 (25.6)	0.81

Values given are n (%).

*Denotes statistically significant at the $\alpha = 0.05$ level.

Table 2. Adjusted effects of non-modifiable and modifiable on infantile atopic eczema among Slovak children

Exposure	OR _{adj} (95% CI)	% Total regression score
<i>Non-modifiable factors</i>		
Family history of atopy	–	9.4
Maternal history of atopy	1.50 (1.1–2.2)*	4.5
Paternal history of atopy	1.64 (1.1–2.6)*	4.9
Parental education	–	13.0
High maternal education	0.98 (0.8–1.3)	3.3
High paternal education	1.27 (1.04–1.5)*	9.7
Pregnancy and fetal factors	–	23.4
Maternal age ≥ 35 yr	2.5 (0.7–2.4)	2.1
High-risk pregnancy	1.39 (0.98–1.9)	2.1
Male gender	1.28 (0.9–1.8)	3.0
Birth order higher than one	1.12 (0.8–1.6)	0.1
Low birth weight	4.03 (0.98–17.4)	1.9
Winter birth	1	–
Spring birth	0.48 (0.3–0.7)*	11.7
Summer birth	0.79 (0.5–1.2)	0.8
Autumn birth	0.86 (0.5–1.5)	1.7
Region type	–	11.3
Rural	1	–
Agricultural	0.46 (0.3–0.8)*	9.3
Industrial	1.33 (0.9–2.1)	2.0
Residential factors	–	4.7
Residence near heavy traffic	1.1 (0.8–1.5)	0.2
Residence in a town vs. village	1.59 (1.05–2.4)*	4.5
Residence in a house vs. flat	0.95 (0.6–1.7)	<0.1
<i>Non-modifiable factors</i>		
Fuel type for heating and cooking	–	1.3
Use of central heat	0.66 (0.4–0.96)	0.1
Use of electricity	1.34 (0.9–1.98)	0.7
Use of coal stove	0.62 (0.3–1.3)	0.4
Use of wood fuel	1.12 (0.6–2.3)	<0.1
Use of gas	0.98 (0.7–1.4)	<0.1
Parental smoking	1.36 (1.01–1.8)*	2.5
Other household exposures	–	1.3
Mold or cockroach problems in the home	0.94 (0.4–2.1)	<0.1
Carpeting or featherbed in the home	1.11 (0.5–2.3)	1.3
Animal ownership	–	5.6
Own cat	2.10 (1.2–3.6)*	1.4
Own other furred pet	1 (0.6–1.6)	<0.1
Own bird	1.33 (0.6–2.8)	0.7
Own livestock	0.55 (0.3–0.9)*	3.5
Infant feeding	–	27.5
Any formula in the first year of life	1.60 (1.04–2.5)*	5.1
Exclusive breast feeding for ≥ 4 months	0.30 (0.1–0.8)*	6.4
Introduction of solid food < 4 months	0.81 (0.6–1.1)	2.4
Cow's milk in the first year of life	1.1 (0.6–2.11)	3.3
Eggs in the first year of life	1.92 (1.2–3.2)*	4.0
Citrus in the first year of life	1.11 (0.7–1.8)	2.3
Fish in the first year of life	1.56 (1.1–2.3)*	4.0
Nuts in the first year of life	1.22 (0.8–1.8)	<0.1

*Denotes statistically significant at the $\alpha = 0.05$ level.

Modifiable factors contributed more to the TRS for those members of the birth cohort with one (46% TRS) or both (50% TRS) parents with atopy (data not shown). Furthermore, the

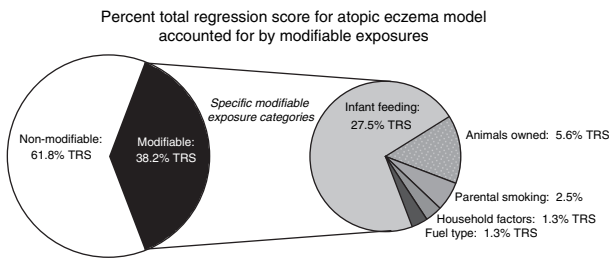


Fig. 1. Percent total regression score for atopic eczema accounted for by modifiable exposures.

modifiable exposure category of infant feeding practices accounted for an increasing proportion of the TRS for those members of the birth cohort with one (29.3% TRS) or both (31.7% TRS) parents with atopy, compared with the 27.5% TRS for the category of infant feeding practices observed for the entire birth cohort.

Discussion

Among this birth cohort of 1326 children from the Slovak Republic, 207 (15.6%) developed AE by 1 yr of age. The non-modifiable exposures of maternal and paternal history of atopy accounted for 4.5% and 4.9% of the TRS, respectively. Three non-modifiable exposure variables accounted for a greater proportion of the TRS than did parental history of atopy: birth in the spring (11.7% TRS) and residence in an agricultural region (9.3% TRS), which were protective, and high paternal education (9.7% TRS). The only modifiable exposure variable that accounted for a greater proportion of the TRS than did parental history of atopy was exclusive breast-feeding for at least 4-months duration (6.4% TRS), which was protective. However, when the variables related to infant dietary and feeding practices were considered together, they accounted for a larger proportion of the TRS (27.5% TRS) than did any other modifiable or non-modifiable categories of exposure.

The prevention of infantile AE is considered a possible approach to asthma prevention (32), given that infantile AE is a risk marker for those who may later develop asthma (25–29). Findings from this study indicate that overall non-modifiable exposures contribute more to the development of infantile AE than do modifiable exposures, but that modifiable exposures become increasingly more important when one or both parents have atopy. Among modifiable exposures, those related to infant diet and feeding practices contribute substantially more to the TRS for infantile AE (27.5% TRS) than do modifiable environmental exposures (10.7% TRS for expo-

sure related to animal ownership, parental smoking, fuel type used for heating or cooking, and other household characteristics combined), and account for a progressively greater amount of the TRS if one (29.3% TRS) or both parents (31.7% TRS) are atopic. Thus, attention to infant diet and feeding practices is likely a worthwhile strategy for the prevention of infantile AE, and may possibly be worthwhile for the prevention of the development of asthma, particularly for those children with a parental history of atopy.

With regard to non-modifiable exposures, our findings are in agreement with those of a European birth cohort study that birth in the spring (29) is protective for infantile AE. The effect of season or month of birth on infantile AE is thought to be mediated by the timing of exposure to high levels of aeroallergens, with resultant sensitization (50, 51). In contrast to other studies, the non-modifiable exposures of male gender (38–40), low birth order (41, 42) or a complicated pregnancy or perinatal course (44, 52) was not found to be significantly associated with infantile AE. However, the relationship for each of these exposures and the development of infantile AE was nearly statistically significant and each was found to be important to retain in the multivariate logistic model.

In this study, exclusive breast feeding for at least 4-months duration was found to be protective for AE, in agreement with other prospective studies that find it is protective for AE through 2 yr of age (53) and older (29, 54, 55). A review of 22 studies assessing the relationship between breast-feeding and AE found seven studies that reported a protective effect while 15 studies did not show an effect (56). A meta-analysis on the topic concludes that there is a significant preventive effect of breast-feeding on AE among children with a family history of atopy and a negative, non-significant effect among children without a family history of atopy (57). Prospective studies as the meta-analysis support these conclusions (58–62).

In this study, no statistically significant relationship was found between AE and the early introduction (<4 months of age) of solid food, in agreement with findings of other prospective studies (62) and in contrast to others (40, 63, 64). Dietary exposure to eggs and fish in the first year was, however, found to be linked to infantile AE in this study. Another birth cohort study found that sensitization to eggs and peanuts is linked to the development of AE by 4 yr of age (40). High-level allergen exposures, particularly to cow's milk, eggs, wheat, citrus, nuts, and fish, may predispose children to allergic sensitization (65).

In this study, cat ownership was found to predispose to infantile AE. Sensitization to cats has been linked to the development of AE (16); however, there is controversy in the literature regarding the role of animal ownership and AE. Pet ownership has been linked with allergic sensitization and aggravation of AE in some studies (66) and with protection from AE in others (67–70). A recent cohort study finds a protective effect of keeping any pet in the first year of life (in particular dogs) and the development of AE in the first 2 yr of life. In the same study, ownership of small furred pets (hamsters, rabbits, and guinea pigs) showed a borderline protective effect, while no effect was ascertained for cat ownership (71). In this study, livestock ownership was found to be protective from infantile AE, consistent with another study that found that living on a farm was protective from the development of AE by 18 months of age (68).

As with other cohort studies (31, 40, 72), the development of AE was found to be influenced by household environmental tobacco smoke. A protective role for the use of central heat in the home was found consistent with findings from another cohort study that central heat decreased the risk of AE (73).

Our study has several strengths. First, a specific case definition for AE was employed, requiring a physician's diagnosis of AE either by study allergists at the 1-yr evaluation (according to SCORAD index) or by another physician at any point during the first year of life (as reported by the mother). Secondly, the prospective cohort design allows for a clear delineation of the temporal sequence of exposure and the outcome of AE. Thirdly, a large number of exposures were assessed – ranging from genetic, pregnancy- and fetal-related, regional and household-level, as well as dietary factors – allowing for the control of several important risk factors (and potential confounders) simultaneously. Importantly, our evaluation of the presence of pregnancy- and fetal-related factors was based upon physicians' review of the maternal medical record. The population-based sample was derived from distinct region types (industrial, agricultural, and rural) such that the role of macro-level exposures could be incorporated into our logistic model. Finally, the logistic model used in the analyses fit the data very well.

A weakness of our study is the loss to follow up (33% of the assembled birth cohort). The percentage of the birth cohort lost to follow up varied significantly by region type ($\chi^2 = 36$; $p < 0.001$): rural regions lost 35%, agricultural regions 22%, and industrial regions 37%. The

loss to follow up was likely because of the lack of incentives for the continued participation of the recruited mother–child dyads. The higher loss to follow up observed in the industrial regions was likely because of greater migration and difficulties with transportation from small villages to regional allergists. Among those lost to follow up, there was no difference in rates of paternal history of atopy or the rates of pregnancy- and fetal-related factors evaluated in this study, when compared with the birth cohort with follow up.

The differential loss to follow up according to region type could have influenced our finding that residence in an agricultural region type was protective for AE if the group lost from the industrial and rural region types disproportionately consisted of those who did not develop infantile AE (the so-called Berksonian bias). However, we have no reason to believe that those who did not develop AE would be less likely to follow up in the industrial and rural region types but not in the agricultural region types, so the Berksonian bias seems unlikely. Furthermore, it has been shown that the Berksonian bias is largely 'self-correcting', and thus rarely an important cause of bias, if persons with a given disease are likely to have greater losses than those without the disease (74).

Further research is necessary to clarify the role region type may play in the development of AE and other allergic diseases. For this study, living in an agricultural region type was found to be protective for infantile AE, while in our previous research it was found to be an important risk factor for cord blood immunoglobulin E positivity (75). Agricultural region type was defined on the basis of heavy farming and the extensive use of chemical fertilizers. One could speculate that living in an agricultural region type was protective because of the higher proportion of families that own livestock in agricultural regions compared with other regions (27.4% vs. 18.4%; $\chi^2 = 13.6$, $p = 0.002$). However, livestock ownership was controlled for in the logistic model. Thus, it seems that other factors unique to residence in an agricultural region type likely account for the protective effect.

Another potential weakness of our study is the self-reported nature of the evaluated exposures (with the exception of pregnancy- and fetal-related factors). With any self-reported data, there is likely to be some misclassification of exposure, although exposures are likely to be misclassified non-differentially, i.e. reported the same by cases and non-cases). Non-differential misclassification of exposure would bias our estimates of effect toward the null value. In the

case of parental smoking, it is established that parents have a tendency to underreport their smoking status (76, 77). As a positive association between parental smoking and AE was found despite any tendency to underreport parental smoking, this is likely to be a true effect.

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