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Prenatal, intrapartum, and postnatal factors are associated with pediatric eosinophilic esophagitis

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Abstract

Background—Multiple lines of evidence point to the potential importance of early-life environmental factors in the rapid increase in the incidence of eosinophilic esophagitis (EoE), but potential exposures have not been extensively studied.

Objective—We sought to assess the association between prenatal, intrapartum, and postnatal factors and the development of pediatric EoE using a case-control study.

Methods—Patients with EoE were recruited from an existing registry at Cincinnati Children's Hospital Medical Center (CCHMC). Population-based community control subjects were identified from a separate CCHMC registry. Mothers of study subjects were contacted and completed a Web-based questionnaire. Crude and adjusted models were used to estimate associations.

Results—Mothers of 127 cases and 121 control subjects were included. We observed a positive association between several early-life factors and EoE, including prenatal (maternal fever: adjusted odds ratio [aOR], 3.18; 95% CI, 1.27–7.98; preterm labor: aOR, 2.18; 95% CI, 1.06–4.48), intrapartum (cesarean delivery: aOR, 1.77; 95% CI, 1.01, 3.09), and infancy (antibiotic use: aOR, 2.30; 95% CI, 1.21–4.38; use of an acid suppressant: aOR, 6.05; 95% CI, 2.55–14.40) factors. We observed an inverse association between having a furry pet in infancy and EoE (aOR, 0.58; 95% CI, 0.34–0.97). No associations were observed for breast-feeding or maternal multivitamin or folic acid supplement use.

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Conclusion—Early-life factors, including maternal fever, preterm labor, cesarean delivery, and antibiotic or acid suppressant use in infancy, were associated with risk of pediatric EoE; having a pet in the home was protective. These results add to growing evidence that implicate early-life exposures in EoE pathogenesis.

Keywords

Allergy; antibiotics; acid suppressant; breast-feeding; cesarean delivery; early-life factors; environment; eosinophilic esophagitis; furred pet; neonatal intensive care unit; acid-suppressive agents

Eosinophilic esophagitis (EoE) has progressed over the past 2 decades from a case-reportable disease (0.4 cases/100,000 person-years) to a major cause of upper gastrointestinal morbidity[1,2] with an estimated incidence of 10 cases/100,000 person-years and a prevalence of 50 to 100 cases/100,000 persons.[3,4] In the United States, where 150,000 to 400,000 persons are affected,[5] the estimated annual health care costs associated with EoE approach $1 billion.[6] Although increased disease recognition is likely a contributory factor to the increase in EoE incidence,[7] environmental factors are also likely contributory,[8,9] as evidenced from twin studies that have disentangled genetics from environment and demonstrated that environmental factors account for nearly 85% of the disease cause.

Patients with EoE often have atopic comorbidities, respond to elimination diets, relapse on food re-exposure, and have a T_H2-like transcriptome response in the esophagus, suggesting that the disease is allergen mediated.[10,11] Furthermore, experimental modeling in mice has shown that esophageal eosinophilia with pathologic features of EoE can be induced by exposing mice to allergens through respiratory, cutaneous, and intraesophageal routes.[12]

Recent research on other atopic diseases has shifted focus on the contribution of environmental risk factors to early-life perturbations believed to lead to dysbiosis in colonization of the gut and subsequent dysregulation in immunity. Independent of dysbiosis, these environmental factors can also lead to epigenetic changes that might lead to disease development. Epigenetic modifications in relation to environmental factors have not been explored in patients with EoE but have been suggested to contribute to the development of other atopic disease conditions.[13] Identified environmental factors of interest for atopic diseases have included mode of delivery[11,14,15]; maternal, intrapartum, and infancy antibiotic use[16,17]; preterm delivery[11,18,19]; and neonatal hospitalization.[20]

To date, only 3 studies have investigated possible early-life determinants for EoE.[9,21,22] All provided general support for the contribution of early-life factors to disease etiology, although different factors were associated, and there was a lack of consistency in results across studies. All 3 studies had small sample sizes and potential for selection bias.[9,21,22] Because control subjects were hospital based, the heterogeneity in results could be attributable to differences in the underlying exposure distribution in the control subjects. If the exposure distribution in control subjects were different from the population from which cases arose, there could be bias.[23] The goal of the present study was to assess the association between prenatal, intrapartum, and postnatal factors and the development of pediatric EoE by using a case-control study with population-based control subject. We aimed to examine a

relatively large number of cases, expand the scope of factors assessed to include factors implicated in other atopic and immune-mediated diseases,[24] and draw on population-based control subjects representative of the catchment population for the tertiary hospital from which cases were derived.

METHODS

We conducted a case-control study. Cases were recruited from children identified through the EoE database at the Cincinnati Center for Eosinophilic Disorders at Cincinnati Children's Hospital Medical Center (CCHMC). All cases were observed to have 15 or more eosinophils/high-power field (hpf) at the diagnostic endoscopy.[25] We used a cumulative sampling approach for selection of control subjects, specifically sampling control subjects from the population of noncases at the time prevalent cases were assembled. Control subjects were recruited from the CCHMC Genomic Control Cohort, a population-based control cohort representative of the greater Cincinnati population.[26,27] Cases and control subjects were identified through a study of genetic factors for EoE that was restricted to non-Hispanic white subjects. Cases and control subjects were less than 18 years of age at the time of enrollment. Mothers of children who were identified were contacted by telephone to confirm eligibility and to assess willingness to participate. After consenting, mothers of subjects were e-mailed the link to complete the survey to assess early-life exposures. All data were recorded electronically and were deidentified.

Exposures were assessed by using an expanded version of the questionnaire developed in our initial study of early-life exposures, which was generated through an interactive process that included cognitive interviewing and testing. [21] Survey domains included prenatal, intrapartum, and postnatal exposures, including those previously demonstrated to be associated with EoE,[9,21,22,28,29] but also assessment of associations with maternal infections, use of acid suppressants in infancy, and exposure to pets in in the home (see Appendix E1 in this article's Online Repository at www.jacionline.org).

Statistical analyses

First, we examined the extent of missing data and distribution of responses to each of the early-life factors of interest. We then examined the demographic distribution of cases and control subjects and described the presence of atopic comorbidities in cases and control subjects.

Next, we used generalized linear models (logit link and binomial distribution) to examine the odds of disease in those exposed relative to those unexposed. We conducted crude and adjusted analyses. For adjustment, we considered maternal factors that could act as potential confounders of the association between early-life exposures in relation to disease development. Specifically, we adjusted for maternal education as a proxy for socioeconomic status because this could act as both an antecedent factor in the exposures assessed and for the diagnosis of EoE.[30] Crude and adjusted odds ratios (aORs) with 95% CIs were reported.

Specific exposures were addressed as follows. Maternal infection was denoted by the presence of a temperature of at least 100.4°F during pregnancy, and the trimester during

which the fever occurred was also recorded. We characterized maternal smoking as any smoking during pregnancy. Folic acid use was characterized as use of any dose of folic acid supplement alone or in addition to a prenatal multivitamin during pregnancy. Prenatal vitamin use was characterized as regular ingestion of any prenatal multivitamin during pregnancy. Although all prenatal supplements likely contain folic acid, the amount of folic acid included varies (typically 400–800 μg). Furthermore, some women might choose to take a folic acid supplement either because they have been instructed to take a higher therapeutic dose (4 mg for women whose offspring are at increased risk of experiencing a birth defect, such as women with type 1 diabetes) or because they cannot tolerate multivitamins. Folic acid used independently of prenatal vitamins is typically a higher dose than that prescribed through use of a multivitamin. We sought to assess whether these higher doses of folic acid could be associated with development of EoE, thus contributing to the mixed evidence to suggest that folic acid supplement use can be associated with atopic disease and expanding this to include assessment of EoE.[31]

Secondarily, we combined prenatal and folic acid supplementation to reflect varying levels of folic acid intake, specifically characterizing whether neither a folic acid supplement nor a multivitamin was taken, whether just a prenatal multivitamin was taken, or whether a folic acid supplement was taken (58 of 60 respondents who reported taking a folic acid supplement reported also taking a multivitamin). Acid suppressant use was characterized as any use of a proton pump inhibitor (PPI), H_2 antagonist, or other acid suppressant in the first year of life. Preterm labor and birth were defined as labor or delivery before 37 weeks of completed gestation. Although we assessed pregnancy complications independently, there were too few responses in any one category, with the exception of preterm labor, to examine these associations independently. Thus we created a single combined category of indication of having experienced a pregnancy complication, which included gestational diabetes; anemia; pre-eclampsia or pregnancy-induced hypertension; eclampsia; chorioamnionitis; hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; hyperemesis; preterm labor; premature rupture of the membranes; or other complication. Admission to the neonatal intensive care unit (NICU) was characterized as any length of stay in the NICU. For examining the association between use of acid suppressants during the first year of life and EoE and to address concerns of possible protopathic bias or bias resulting from the potential that PPIs were used to address symptoms associated with undiagnosed EoE, we restricted our case sample to those children with symptoms of EoE beginning at age 3 or older. Antibiotic use was restricted to reported administration during the first 12 months of life. Breast-feeding was characterized as any breast-feeding. Pets were restricted to having a pet with fur (ie, dogs, cats, and rabbits) in the home during infancy.

Because we noted that cases arose from a region broader than the greater Cincinnati area, we performed a secondary analysis using the χ^2 test to assess for differences in the exposure distribution between those who resided within or outside of the greater Cincinnati area. Where there were sparse data (count of ≤5), we used the Fisher exact test.

Secondary analysis

Exposures examined could be associated with one another (eg, preterm birth and NICU admission), and the direct effect of each exposure might not be fully estimable. We conducted secondary analyses, adjusting for those related factors that might act as mediators as a means of estimating the direct effect and under the assumption that no factors were confounding the association between the exposure and the mediator.[32] We specifically focused on maternal fever (mediated by preterm delivery and delivery route) and NICU admission (mediated by antibiotic use and an acid suppressant in infancy). The study was approved by the CCHMC Institutional Review Board.

RESULTS

Demographics

Of the 237 cases contacted successfully, 169 (71%) consented to participation. Of these subject-mother pairs, 136 (80%) mothers completed the questionnaire. Similarly, for control subjects, of the 208 potential subjects successfully contacted, 147 (71%) consented to participation, and of these subject-mother pairs, 125 (85%) mothers completed the questionnaire (Fig 1). An examination of the mean age among those who did and did not consent (of all those that were eligible) among both cases and control subjects suggested that unselected cases and control subjects were comparable with those who responded. The mean age of those EoE cases who were not enrolled was 11.1 (SD, 3.4) (compared with 10.6 [SD, 3.8] enrolled), and the mean age of control subjects not enrolled was 12.9 (SD, 2.8; compared with 13.8 [SD, 2.8] enrolled). Our complete case analytic sample included 127 cases and 121 control subjects (Fig 1). The demographic features of the cases and control subjects were similar, with the exception of atopic disease comorbidities and sex (Table I). Consistent with the descriptive epidemiologic literature on EoE,[5,11] cases had a higher prevalence of atopic disease than control subjects, particularly food allergies (83.3% of cases vs 12.4% of control subjects, respectively), and were more likely to be male (80.3% of cases vs 52.1% of control subjects).

Prenatal factors

We observed a strong association between maternally reported fever during pregnancy and risk of EoE (aOR, 3.18; 95% CI, 1.27–7.98; Table II). Although data were too sparse for estimating trimester-specific associations, the distribution of fevers was clustered in the second trimester for cases, with mothers reporting a fever in the second trimester for 11 (9%) cases versus 1 (1%) control subject. We observed no association of maternal smoking or prenatal vitamin use with risk of EoE. We observed a nonsignificant positive association between folic acid use and EoE (aOR, 1.56; 95% CI, 0.86–2.83). Although the odds of EoE among those consuming both a multivitamin and folic acid was higher than the odds of EoE for those using only one or the other, the associations were not significant (data not shown). Analysis of possible trend for association across possible increase in dose was also not significant (P for trend = .10). Preterm labor was positively associated with EoE (aOR, 2.18; 95% CI, 1.06–4.48; Table II), as were pregnancy complications (aOR, 1.87; 95% CI, 1.12–3.12; Table II). Without preterm labor included, the association was attenuated (aOR, 1.29; 95% CI, 0.99–1.69).

Intrapartum factors

Cesarean delivery, compared with vaginal delivery, conferred a 77% increase in risk of EoE (aOR, 1.77; 95% CI, 1.01–3.09). A nonsignificant positive association was observed between preterm birth and EoE (aOR, 1.39; 95% CI, 0.71–2.72; Table III).

Infancy factors

We observed a suggestive association between NICU admission and EoE, although this did not reach significance (aOR, 1.92; 95% CI, 0.95–3.89). Use of antibiotics in infancy was positively associated with EoE (aOR, 2.30; 95% CI, 1.21–4.38). Having a dog or cat in the home during infancy was inversely associated with EoE (aOR, 0.58; 95% CI, 0.34–0.97); no subjects reported having pet rabbits. We observed no association between breastfeeding and EoE. Report of acid suppressant use in infancy was strongly associated with EoE (aOR, 7.41; 95% CI, 4.00–13.74). Restricting the case sample to those reporting symptoms at age 3 years or older had minimal effect on the association observed (aOR, 6.05; 95% CI, 2.55–14.40). Nearly half of the cases reporting development of EoE symptoms at age 3 years or older reported receiving an acid suppressant during infancy (Table IV).

None of the control subjects were from outside of the greater Cincinnati area. For cases, examining the distribution of exposures in those residing within and outside of the greater Cincinnati area identified no significant differences in exposure distribution for all of the early-life factors examined, with the exception of maternal smoking; there was a significantly higher proportion of smokers among cases from within the Cincinnati area (see Table E1 in this article's Online Repository at www.jacionline.org). As an additional analysis, to account for this difference in exposure distribution, we examined the association between maternal smoking and EoE, restricting the case sample to those within greater Cincinnati only. Within this subsample, the association between maternal smoking and EoE still did not reach significance (aOR, 2.06; 95% CI, 0.65–6.48). The results of all the exposures examined are summarized in Fig 2.

Secondary analysis

We attempted to disentangle the effects of related mediating factors by adjusting for these factors. For the association between maternal fever and EoE, further adjustment for preterm birth and delivery route attenuated the observed association slightly (aOR, 2.94; 95% CI, 1.16–7.44). For NICU admission, adjustment for antibiotic use and use of an acid suppressant in infancy attenuated the association observed (aOR, 1.12; 95% CI, 0.33–3.77).

DISCUSSION

The present study is the largest to date examining the associations between early-life factors, including those in the prenatal, intrapartum, and postpartum period, and pediatric EoE and selecting population-based control subjects designed to be representative of the catchment area from which cases arose. Here we report that EoE risk is (1) positively associated with several prenatal exposures, including maternal fever (aOR, 3.18) and preterm labor (aOR, 2.18); (2) positively associated with cesarean delivery (aOR, 1.77); (3) positively associated with antibiotic use during infancy (aOR, 2.30); (4) dramatically and positively associated

with use of acid suppression therapy during infancy (aOR, 6.05); (5) negatively associated with having a furred pet in the home during the postnatal period (aOR, 0.58); and (6) not apparently associated with breast-feeding, maternal multivitamin, or folic acid supplement use. Accounting for possible mediating factors in the association between maternal fever and EoE had no substantive effect on the estimates observed, whereas adjustment for antibiotic and acid suppressant use suggested no independent effect of NICU admission on the risk of EoE. This analysis assumes that the direct effect can be estimated, which might not be a reasonable assumption in the present study if there are confounding factors associated with the exposure and mediating factor or factors.[32]

A strength of the current study is the use of population-based control subjects from the catchment area of the hospital from which cases were identified, although we note that cases arose from a larger catchment area, possibly because of the relative rarity of EoE. As with 2 of the 3 previous studies conducted on early-life factors and EoE,[9,21] we observed positive associations between both cesarean delivery and antibiotic use in infancy with EoE. No association was observed with folic acid supplement use or use of a prenatal multivitamin; however, the lack of available data on folic acid dose might make these results less interpretable. Although a suggestive inverse association between breast-feeding and EoE had been noted previously,[21] this association was observed in neither the present study nor the other 2 studies conducted to date.[9,22] The inverse association previously noted for smoking[22] was also not observed. However, this inverse association had been observed for postnatal environmental tobacco smoke exposure only, whereas in the present study we examined prenatal exposure only.

Antibiotics and cesarean delivery have been demonstrated to alter colonization of the gut in early life.[33] Although some studies suggest that these changes can be transient, early infancy is a period of unique susceptibility for immune development. Colonization of the gut microbiota in early life is essential to establishing the mucosal barrier, developing tolerance, and promoting immune maturation.[34,35] It is notable that the 2 main EoE susceptibility genes, *TSLP* and *CAPN14,* are genes encoded by the mucosal epithelium, which would presumably be the tissue to directly encounter microbial content. In addition, *CAPN14* has been shown to regulate esophageal barrier function, which presumably affects the extent of exposure to the environmental factors identified.[36]

We also observed several novel positive associations of preterm labor, maternal fever, and pregnancy complications with EoE. Maternal fever has been implicated as a possible contributing factor in patients with other atopic illnesses,[37] and fetal exposure to proinflammatory cytokines, as a result of maternal infection, might interfere with the development of the fetal immune system.[38] Pregnancy complications, including pre-eclampsia, have been associated with atopic illnesses.[37,39] Pre-eclampsia is associated with increased maternal proinflammatory cytokines, which might contribute to an altered immunologic development in the fetus.[40] The inverse association with pet exposures has been observed in studies of other atopic illnesses,[41] although the evidence is mixed, with some studies suggesting a protective association for cats, dogs, or both and other studies suggesting no association.[42]

Interestingly, the strongest new association we observed was for infant use of an acid suppressant. Although this association might simply reflect treatment of early EoE symptoms,[43,44] there is some evidence in support of a causal association, especially when given in early life.[45–48] Animal models, clinical studies, and observational studies suggest that antisecretory agents might act to incite an inappropriate immune response through direct alteration of the gut mucosal permeability or through interference with normal digestion of dietary proteins, thus preserving antigens that induce a T_H2 response.[48] In both animal[49,50] and human[51] studies, antisecretory agents have promoted IgE formation toward dietary antigens. Conversely, some studies have suggested that an overabundance of acid might impair esophageal barrier function[52] and that PPIs can, in some instances, restore esophageal barrier function.[53]

Although the number of cases included in this study was the largest assembled to date, an even larger sample size would facilitate characterizing the environmental factors with a higher degree of detail. Moreover, exposures were characterized based on maternal recall. Given that these exposures occurred roughly a decade earlier, there is the potential for recall bias. However, some factors, such as cesarean delivery, breast-feeding, preterm birth, NICU admission, and maternal smoking, are unlikely to be hampered by recall.

Although there were minimal missing data across most exposures (Table I), responses for antibiotic use and fever during pregnancy had more than 10% missing. For antibiotic use, missingness was roughly comparable between cases and control subjects (17% vs 14% missing, respectively). If those missing a response were all assumed to be unexposed, the estimate would have attenuated to an odds ratio of 1.66 (95% CI, 0.99–2.79). For maternal fever, mothers of cases were less able to recall exposure to fever during pregnancy (25% cases vs 15% control subjects missing). Assuming all of these were indicative of no exposure to maternal fever, the estimate would have attenuated to an odds ratio of 2.46 (95% CI, 1.03–5.85). Although this provides some reassurance that the qualitative positive association observed for antibiotic use and maternal fever is not likely an artifact of selection bias, the potential remains that the inability to recall is associated with both exposure status and case status and could reflect a biased estimate. For antibiotic use, there is also the potential that the association observed could be attributed to confounding by indication, whereby some unknown factor is contributing to the use of antibiotics and is also associated with development of EoE. For acid suppressant use, there remains the potential for protopathic bias. The mean age of diagnosis among our cases was 4.9 (SD, 3.5) years. We restricted this analysis to cases in which symptoms were reported at age 3 years or older. However, it remains possible that these children received an acid-suppressive agent as a result of very early and unrecognized manifestations of disease.

Roughly 30% of those eligible for contact were successfully consented for participation, and of these, 80% to 85% completed the questionnaire. Although the success rate for enrolling subjects was comparable across cases and control subjects, there is the potential that those participating represent a selected population no longer representative of the population eligible for participation. Furthermore, the sample of cases and control subjects was restricted to non-Hispanic white subjects. Although EoE is more commonly diagnosed in

white subjects,[54] this might limit the generalizability of the study findings to other racial and ethnic groups.

In our study cases had a median of 50 eosinophils/hpf (interquartile range, 37.5–96.0 eosinophils/hpf). However, we do not have any other histologic or clinical data by which disease severity could be characterized.[55] Peak eosinophil count per hpf has been demonstrated to correlate poorly with disease symptoms,[55,56] and thus we were not able to characterize exposures in relation to disease severity. Additionally, we did not restrict our cases to those who underwent a PPI trial before diagnostic endoscopy. PPI use before diagnosis was not a discriminating factor in our 2 prior genome-wide association studies,[27,57] and the mechanistic factors for EoE and PPI-responsive esophageal eosinophilia are believed to overlap.[58] Finally, clinical and histologic data suggest no differences between EoE and PPI-responsive esophageal eosinophilia.[59]

In conclusion, the present study is the largest to date examining the associations between early-life factors, including those in the prenatal, intrapartum, and postpartum periods, and pediatric EoE. We report that EoE risk is (1) positively associated with several prenatal exposures, including maternal fever (aOR, 3.18) and preterm labor (aOR, 2.18); (2) positively associated with cesarean delivery (aOR, 1.77); (3) positively associated with antibiotic use during infancy (aOR, 2.30); (4) dramatically and positively associated with use of acid suppressant therapy during infancy (aOR, 6.05); (5) negatively associated with having a furred pet in the home during infancy (aOR, 0.58); and (6) not apparently associated with breast-feeding or maternal multivitamin or folic acid supplement use. Because many of the factors identified in this study are potentially modifiable, our findings have implications for prevention. On a clinical level, patients exposed to the identified environmental factors might receive differential evaluations for EoE based on the particular risk factor's association. Further studies focused on gene-environment interactions might improve the predictive value of these exposures; specifically, patients who harbor certain genetic variants in EoE susceptibility genes can have differential responses to each environmental factor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

aOR	Adjusted odds ratio
CCHMC	Cincinnati Children's Hospital Medical Center
EoE	Eosinophilic esophagitis
HELLP	Hemolysis, elevated liver enzymes, and low platelet count
hpf	High-power field
NICU	Neonatal intensive care unit
PPI	Proton pump inhibitor

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Key messages

- Heritability estimates for EoE suggest that both genetics and early-life environmental factors are implicated in disease pathogenesis.
- Prenatal (maternal fever, preterm labor), intrapartum (cesarean delivery), and postnatal (antibiotic use and use of acid-suppressive agents) factors are associated with increased risk of EoE (aOR, 1.8–6.1). In contrast, having a furred pet in infancy was protective against EoE (aOR, 0.6).
- Identifying modifiable factors for disease risk not only offers the potential opportunity to develop a further understanding of the pathogenesis of disease but also opportunities for modifying disease development.

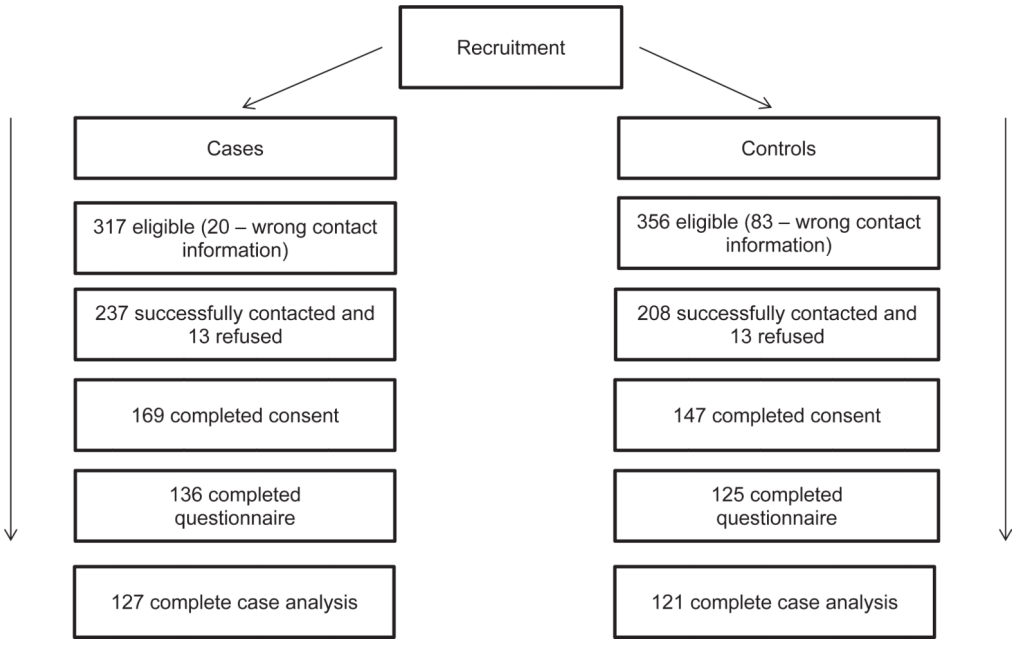

FIG 1.
Recruitment of cases and control subjects and final study sample.

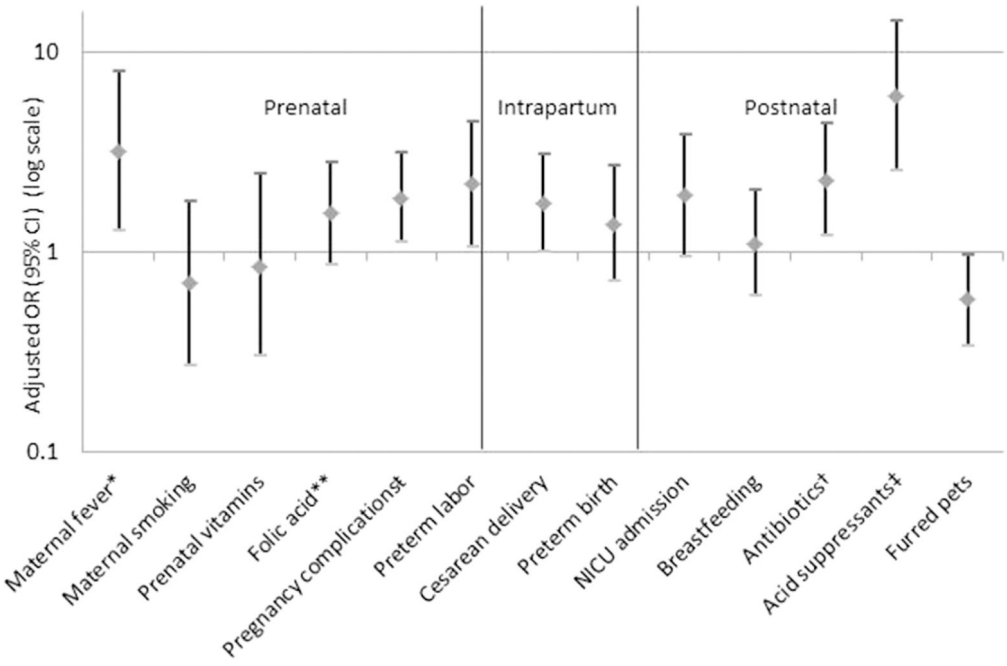

FIG 2.

Association between prenatal, intrapartum, and postnatal factors and EoE. *Sample was reduced to 98 cases and 102 control subjects because of missing data; fever was defined as having a temperature of >100.4°F. **Characterized as use of a folic acid supplement independent of any use of a prenatal vitamin. ‡Includes gestational diabetes, anemia, pre-eclampsia or pregnancy-induced hypertension, eclampsia, chorioamnionitis, HELLP syndrome, hyperemesis, preterm labor, premature rupture of the membranes, or other complication. †Sample was reduced to 105 cases and 107 control subjects because of missing data. ‡Restricting analysis to those reporting symptoms at age 3 years or later for cases (n = 37); there were missing data on 4 control subjects.

TABLE I.

Characteristics of the study population

Characteristic	Control subjects, n = 125, (% or mean [SD])	Cases, n = 136 (% or mean [SD])
Age at enrollment (y), mean (SD)	13.8 (2.8)	10.6 (3.8)
Sex (% male)	52.1	80.3
Atopic illnesses (%)		
Food allergies	12.4	83.3
Environmental allergies	42.2	69.3
Antibiotic allergies	14.5	25.8
Eczema	21.5	59.1
Asthma	18.2	44.9
Maternal marital status (%)		
Married or civil union	93.6	91.9
Single	6.4	5.9
Missing	0.0	2.2
Maternal education (%)		
<HS	0.0	2.2
HS or GED	17.6	11.0
Technical or Associate's degree	20.8	18.4
Bachelor's degree	39.2	35.3
Graduate or professional	20.0	27.9
Missing	2.4	5.2
Maternal smoking (%)		
Yes	9.6	5.9
No	90.4	94.1
Missing	0.0	0.0
Folic acid supplements (%)		
Yes	20.0	27.9
No	80.0	71.3
Missing	0.0	0.7
Prenatal vitamin supplements (%)		
Yes	94.4	94.1
No	5.6	5.9
Missing	0.0	0.0
Maternal fever (%)		
Yes	6.4	14.7
No	78.4	60.3
Missing	15.2	25.0
Preterm labor (%)		
Yes	11.2	20.6
No	88.8	79.4
Missing	0.0	0.0

Characteristic	Control subjects, n = 125, (% or mean [SD])	Cases, n = 136 (% or mean [SD])
Preterm delivery (%)		
Yes	14.4	19.1
No	84.8	80.2
Missing	0.8	0.7
Pregnancy complications (%)*		
Yes	40.0	54.4
No	59.2	44.9
Missing	0.8	0.7
Cesarean delivery (%)		
Yes	22.4	36.0
No	77.6	64.0
Missing	0.0	0.0
NICU admission (%)		
Yes	11.2	20.6
No	88.8	79.4
Missing	0.0	0.0
Breast-feeding, any (%)		
Yes	76.0	80.2
No	24.0	19.9
Missing	0.0	0.0
Antibiotic use in infancy (%)		
Yes	57.6	66.9
No	28.8	15.4
Missing	13.6	17.7
Acid suppressant use in infancy (%)		
Yes	14.4	55.9
No	82.4	42.7
Missing	3.2	1.5
Furry pet in infancy (%)		
Yes	54.4	45.6
No	45.6	54.4
Missing	0.0	0.0

GED, General Education Development test certification; *HS*, high school.

*Includes gestational diabetes, anemia, pre-eclampsia or pregnancy-induced hypertension, eclampsia, chorioamnionitis, HELLP syndrome, hyperemesis, preterm labor, premature rupture of the membranes, or other complication.

TABLE II.

Association between prenatal factors and EoE

Prenatal factor	Control subjects (n = 121)	Cases (n = 127)	OR	aOR*
Maternal fever†				
No	95	79	Referent	Referent
Yes	7	19	3.26 (1.31–8.16)	3.18 (1.27–7.98)
Maternal smoking				
No	110	119	Referent	Referent
Yes	11	8	0.67 (0.26–1.73)	0.70 (0.27–1.80)
Prenatal vitamin use				
No	7	8	Referent	Referent
Yes	114	119	0.91 (0.32–2.60)	0.85 (0.30–2.45)
Folic acid supplement use‡				
No	97	91	Referent	Referent
Yes	24	36	1.60 (0.89–2.89)	1.56 (0.86–2.83)
Pregnancy complications§				
No	72	58	Referent	Referent
Yes	46	68	1.84 (1.10–3.05)	1.87 (1.12–3.12)
Preterm labor				
No	108	101	Referent	Referent
Yes	13	26	2.13 (1.04–4.39)	2.18 (1.06–4.48)

*Includes adjustment for maternal education.

†The sample was reduced to 98 cases and 102 control subjects because of missing data. Fever was defined as having a temperature of >100.4°F.

‡Characterized as use of a folic acid supplement independent of any use of a prenatal vitamin.

§Includes gestational diabetes, anemia, pre-eclampsia or pregnancy-induced hypertension, eclampsia, chorioamnionitis, HELLP syndrome, hyperemesis, preterm labor, premature rupture of the membranes, or other complication.

TABLE III.

Association between intrapartum factors and EoE

Intrapartum factor	Control subjects (n = 121)	Cases (n = 127)	OR	aOR*
Mode of delivery				
Vaginal	93	83	Referent	Referent
Cesarean	28	44	1.76 (1.01–3.08)	1.77 (1.01–3.09)
Preterm birth				
No	103	103	Referent	Referent
Yes	18	24	1.33 (0.68–2.60)	1.39 (0.71–2.72)

*Includes adjustment for maternal education.

TABLE IV.

Association between Infancy factors and EoE

Infancy factor	Control subjects (n = 121)	Cases (n = 127)	OR	aOR*
NICU admission				
No	107	101	Referent	Referent
Yes	14	26	1.97 (0.97–3.98)	1.92 (0.95–3.89)
Breast-feeding, any				
No	28	26	Referent	Referent
Yes	93	101	1.17 (0.64–2.14)	1.11 (0.60–2.05)
Antibiotic use (infancy)†				
No	35	19	Referent	Referent
Yes	70	88	2.32 (1.22–4.40)	2.30 (1.21–4.38)
Acid suppressant use (infancy)‡				
No	99	19	Referent	Referent
Yes	18	18	5.21 (2.30–11.80)	6.05 (2.55–14.40)
Cats or dogs in home (infancy)				
No	40	58	Referent	Referent
Yes	81	69	0.59 (0.35–0.98)	0.58 (0.34–0.97)

*Includes adjustment for maternal education.

†Sample was reduced to 105 cases and 107 control subjects because of missing data.

‡Restricting analysis to those reporting symptoms at age 3 years or later for cases (n = 37); there were missing data on 4 control subjects.