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Environmental risk factors and early life exposures for Juvenile Idiopathic Arthritis; a case: control study

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Abstract

Objective—Juvenile Idiopathic Arthritis (JIA) is a heterogeneous group of disorders characterized by chronic arthritis in children with unknown etiology. Although research evaluating environmental or early life exposures in JIA is scarce, there are data to suggest a role for infections, smoking exposure and lack of breastfeeding. This case-control study investigated the association of selected environmental and early life risk factors with development of JIA.

Methods—JIA cases were identified at a major pediatric rheumatology outpatient clinic. Each case was asked to identify up to three healthy playmates of similar age and gender to serve as controls. Parents/ caregivers of cases and controls completed a questionnaire on selected environmental and early life exposures. Conditional logistic regression adjusted for age and socioeconomic status was used to determine odds ratio (OR) for developing JIA with 95% confidence intervals (CI) for the playmate-matched design.

Results—225 JIA cases and 138 controls were included. Compared to playmate-matched controls pre-term delivery (OR 1.8, 95% CI: 1.2 –2.7) was associated with JIA. There was no association between JIA and household smoking or maternal prenatal smoking, breastfeeding, hospitalization with infection in first year of life, daycare attendance before 6 years of age, household pets or residential area prior to onset of JIA.

Conclusion—There was no association between previously reported risk factors of smoking, early life infection or breastfeeding and development of JIA in this study. The association of pre-term delivery with JIA needs to be further studied.

Keywords

juvenile arthritis; environmental risk factors; case-control study

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Introduction

Environmental factors that act as triggers in a genetically susceptible host are postulated to be a contributing factor in the etiology of juvenile idiopathic arthritis (JIA). JIA is a group of seven mutually exclusive categories of chronic arthritis (1) with unknown etiology in children younger than 16 years of age. Systematic research on environmental risk factors is scant in JIA due to logistic and methodological challenges including rarity of disease, absence of population-based databases, change in disease category over time, small numbers for sufficient power analysis in individual JIA categories, lack of sensitive and specific measures of exposure quantification and difficulties in identifying controls. Previously investigated and proposed environmental risk factors for JIA vary and include infections, smoking, stressful events, perinatal characteristics and lack of breast-feeding. A Swedish population based case: control study noted increased risk of JIA with infections in the first year of life (2); however, this study included only hospitalized JIA cases. An Australian case: control study did not find any association with breast feeding or prenatal smoking but noted an inverse relationship between paternal smoking and JIA that the authors attributed partly to changes in parent behavior (3). This case-control study utilized a questionnaire to assess the association between selected environmental/ early life exposures with development of JIA.

Methods

The study was conducted at a major regional pediatric rheumatology clinic and was approved by the requisite Institutional Review Board for Protection of Human Subjects. Cases included children diagnosed with JIA by board-certified pediatric rheumatologists during routine rheumatology outpatient clinic visits in 2013. Enrolled JIA cases were asked to identify up to three healthy playmates of similar age and gender that served as controls. Parents/ caregivers of cases and controls completed a one page structured (total 15 questions) questionnaire on environmental/ early life risk factors in reference to a predetermined time period of one year before JIA symptom onset for cases and a similar calendar year for controls.

The questionnaire enquired about demographic details including age of child at time of survey, maternal and paternal age, body mass index (calculated from weight and height) at time of survey and annual house-hold income as a proxy for socio-economic status (<25,000, 25,000–49,999, 50,000 –74,999, 75,000–99,999, 100,000–150,000, >150,000 $/ year). Based on literature review (2–8) the following categories of environmental risk factors were investigated with the questionnaire: perinatal delivery characteristics including: birth weight (lbs), mode of delivery (vaginal, forceps/vacuum, C-section), gestational age (pre-term <37 weeks, term 37–41 weeks and post-term >41 weeks) and place of delivery (home, hospital/ birthing center), cigarette smoke exposure (mother/ father/ relative; inside versus outside house; average number of cigarettes smoked per day), maternal prenatal smoking (average number of cigarettes/ day, average number of months during pregnancy smoked), breastfeeding (yes/no and duration), introduction of cow’s milk into diet (before 1 year, after 1 year of age), exposure to early life infections (hospitalization within first year of life, day-care attendance before 6 years of age, household pets and birth order), stressful live events

(death in family, divorce/separation in family, move, new school, unemployment) and residential area (urban, rural and residential move since diagnosis, defined as: urban - encompasses at least 2,500 people of which 1,500 reside outside institutional group quarters, rural - includes open country and settlements with < 2,500 residents). Surveys were administered on paper forms and subsequently transcribed into electronic format using REDCap electronic data capture tools (9) hosted at the Institute for Translational Health Sciences, University of Washington/ Seattle Children's Hospital. To minimize data entry errors checkpoints were placed in the REDCap database and 10% of data entry was randomly checked by another investigator for errors. Chart review was used to complete selected available missing socio-demographic information for case participants.

Analysis

Participant characteristics were descriptively summarized separately for cases and original playmate-matched controls. To assess the degree of over-matching (secondary to the use of playmate controls), we calculated the frequency and percentage of exact case-control matches for each variable of interest. Frequencies and percentages were calculated for discrete variables, means and standard deviations for continuous variables, or median and interquartile range (IQR) for markedly skewed variables. In primary analyses, cases and playmate-matched controls were analyzed by conditional logistic regression (reported as odds ratios (OR) and associated 95% confidence intervals (CI)) separately for each risk factor of interest (a) unadjusted and (b) adjusted for covariates age at the time of survey and annual household income. To minimize potential over-matching in the original playmate-matched cohort, a sensitivity analysis was conducted using a frequency-matched age and gender subset of controls selected randomly using an algorithm developed previously at University of Washington (10). Frequency matching was based on gender and age at the time of survey. Analyses were repeated for cases and *post hoc* frequency-matched controls using logistic regression (data not shown). Statistical analyses were conducted using STATA 12.0 (StataCorp LP, College Station, TX, USA).

Results

A total of 356 eligible subjects were approached for the study of whom 127 (36%) declined to participate. We did not investigate the reasons for why participants chose to decline to enroll for the study. Three enrolled cases were excluded as they were adopted and 1 was enrolled twice in error. At least one playmate-matched control participant responded for each of 80 (37.8%) cases, with responses from as many as 3 controls per case for 11 (4.9%) cases. Among categorical variables, the frequency of exact matches ranged from 29.6% (40/135 pairs) for annual income to 98.5% (133/135 pairs) for variables including maternal and paternal smoking inside the house. Final analysis was conducted on 225 JIA cases, 138 playmate-matched controls and 99 *post hoc* frequency-matched controls.

Missing or declined to answer data for the questionnaire was as follows: no or <1% missing data for age at time of survey, gender, birth order, hospitalization with infection, breastfeeding, daycare attendance, mothers marital status, household smoking, pets and residential area; 2–5% for race, ethnicity, mode of delivery, maternal age, marital status; 6–

10% for paternal age; 10–15% for annual household income, gestational age, birth-weight and place of delivery. 16% of controls did not answer body mass index (BMI) data compared to only 1% of cases. 23% of controls and 7% cases did not remember if cow's milk was introduced at less than 1year of age.

Mean participant age at the time of survey was 11.1 years (IQR 8 to 15 years). Cases were predominantly female (70.7%), non-Hispanic (90.2%), and Caucasian (84.9%). JIA cases were more likely to be born pre-term, to be exposed to cow's milk after one year of age or to live in a rural area (Table 1). The distribution of JIA categories was as follows: polyarticular JIA rheumatoid factor negative 78 (35%), oligoarticular JIA 43 (19%), extended oligoarticular JIA 41(18%), enthesitis related arthritis 26 (12%), psoriatic 17 (7%), systemic 11 (5%) and polyarticular rheumatoid factor positive 9 (4%).

Risk Estimates

The odds of JIA for identified environmental risk factors are outlined in Table 2. Overall the risk estimates and patterns of association between playmate-matched and *post hoc* frequency-matched controls were similar however mode of delivery, gestational age and BMI were no longer significantly associated (results not shown). Females had significantly increased odds of JIA OR 1.8 (95% CI: 1.3 – 2.6). When median income (50,000 – 74,999 $/year) was used as the reference families with incomes of 100,000 – 150,000 $/year had increased unadjusted odds of developing JIA (OR 1.4, 95% CI: 1.0 – 2.1).

Perinatal characteristics

Birth weight, mode of delivery or place of delivery were not associated with development of JIA. However, pre-term babies were at significantly higher risk of developing JIA with OR 1.8 (95% CI: 1.2 – 2.7, p-value <0.01).

Other risk factors

There was no association between household smoking and JIA OR 0.8 (95% CI: 0.5 – 1.4, p-value 0.44). Approximately 5% of mothers smoked during pregnancy among cases and controls with OR 0.8 (95% CI: 0.3 – 2.7, p-value 0.74). Maternal smoking overall had OR 1.8 (95% CI: 0.5 – 6.3, p-value 0.39).

Breastfeeding and duration of breastfeeding were not associated with JIA. There was also no association between cow's milk introduction before 1 year of age and JIA.

There were increased OR with early infection exposure and subsequent development of JIA but none of these achieved significance including hospitalization for infection in the first year of life OR 2.1 (95% CI: 0.8 – 5.6), daycare attendance < 6 years of age OR 1.1 (95% CI: 0.6 – 1.8) and presence of at least one household pet OR 1.2 (95% CI: 0.7 – 1.9).

While the overall presence of stressors in the family in the year prior to JIA symptom onset was not associated with development of JIA (OR 0.8, 95% CI: 0.5 – 1.3), the presence of certain stressors in the family including death and unemployment, were associated with lower odds of developing JIA (death OR 0.3, 95% CI: 0.1 – 0.9, unemployment OR 0.2, 95% CI 0.1 – 0.6).

Rural residence was not associated with JIA, OR 1.2 (95% CI: 1.0 – 1.9). Obesity (BMI 30+) was associated with significantly increased odds of JIA OR 3.9 (95% CI: 1.8 – 8.3).

Two subgroup analyses were conducted to assess the robustness of findings. To address recall bias, we limited the sample to cases with diagnosis within last two years (n=54 cases) and associated playmate-matched controls (n=32). Additionally, we examined polyarticular rheumatoid factor negative (n=78, largest JIA category) and associated playmate-matched-controls (n=28). The results of these analyses were consistent with findings in the overall sample.

Discussion

This study systematically and simultaneously evaluated several environmental and early life exposures one year prior for possible associations with development of JIA. Prematurity was the only risk factor identified in this study associated with increased odds of JIA. The remainder of studied risk factors were not associated with increased JIA risk including cigarette smoke exposure, early life infections, pets, breastfeeding, residential area, stressful life events and other perinatal characteristics. Previous studies from Sweden (2) and Australia (3) examined similar exposures however despite overlap in exposures studied, this study includes a substantially different population and provides external validation of previous findings. This study included a broader representation of JIA identified through outpatient rheumatology clinics (rather than hospital billing codes) at a major regional hospital, where cases are diagnosed by board certified pediatric rheumatologists.

Pre-term delivery was associated with a modestly increased risk of JIA in our study. This contrasts with Carlens et al who showed no association between prematurity and JIA but showed increased risk of JIA with post-term gestational age (OR 1.2, 95% CI 1.0 – 1.34). Similar to them our study found no association between other perinatal characteristics such as birth weight, mode or place of delivery and JIA (2). Prematurity has been linked to later onset of other autoimmune diseases like diabetes; mechanisms implicated include structural changes in organs and epigenetic mechanisms (11). Mechanistic reasons for the observed association of prematurity and JIA are unclear and should be further evaluated.

We have previously reported that maternal smoking is not associated with increased risk of JIA (OR 0.71, 95% CI: 0.58 – 0.87), a relationship that may be confounded by socio-economic status (12). This study prospectively collected data on maternal smoking and socio-economic status (annual household income) and documents no increased risk of JIA with prenatal smoking (OR 0.8, 95% CI: 0.3 – 2.7). This is unlike adult data in which personal smoking is a risk factor for seropositive rheumatoid arthritis (13). Additionally, we were able to evaluate the effect of household smoking of various family members and found no significant association between secondhand smoking and JIA. Similar to adult data it is possible that the effect of smoking may be restricted to certain JIA categories; however, small numbers in individual categories precluded us from studying this further. Since the majority of JIA is seronegative it is plausible and in keeping with adult data that smoking may not play a role in the development of seronegative JIA.

Carlens et al showed increased risk of JIA with early life infections (OR 1.9, 95% CI 1.7 – 2.1) using a case: control design identifying severe cases through hospitalized ICD JIA billing codes (2). In contrast, we found no association with hospitalization for infection in the first year of life or daycare attendance < 6 years and JIA. Differences noted between the studies may be inherent to study design and population studied.

Stress and chronic diseases like JIA have a complex relationship. We showed no relationship between stressful life events overall and JIA. However, interestingly our study showed a significant protective effect for JIA with death in family (OR 0.3, 95% CI: 0.1 – 0.9) and unemployment in the household (OR 0.2, 95% CI; 0.1 – 0.6). Reasons for this protective association are not clear and contrary to previous studies that show stressful events predispose to JIA (14).

The association between obesity and JIA with OR 3.9 (95% CI: 1.8 – 8.3) observed in this study should be approached with caution. Our survey documented BMI at the time of survey completion; hence, obesity does not antedate JIA onset. Reverse causality should be considered, as JIA patients may more likely be obese due to decreased physical activity from active disease or medications such as corticosteroids.

Advantages of our study include a large number of JIA cases and control participants and use of a questionnaire that addressed a broad range of environmental/ early life exposures. We were able to analyze the cigarette smoke exposure and JIA relationship more closely in this prospective study and overcome some of the limitations of our previous study (12), reiterating that there is unlikely a link between prenatal smoking or secondhand smoking and JIA. Limitations include selection bias as we identified JIA cases through outpatient rheumatology clinics and recall bias (sensitivity analysis tried to overcome this limitation). Our control group was not ideal as these were playmates recruited and identified through JIA cases. During the study period we found it difficult to recruit controls as presumably cases would forget/ be less inclined to give questionnaires out to their playmates. Additionally, controls are often less invested in studies thus failing to mail in/return completed questionnaires. We attempted to correct for overmatching of environmental risk factors in the analysis by repeating analyses with a frequency-matched control cohort; however, results were overall similar to original playmate-matched controls. While not ideal, we assumed the critical time period for influence of environmental factors would be a year within onset of JIA symptoms. Due to small numbers in each category, we could not calculate category specific risks (except for polyarticular rheumatoid factor negative JIA) for individual environmental factors.

Conclusion

In keeping with our previous study, findings from this study also do not demonstrate an association between maternal prenatal smoking and secondhand smoke exposure with JIA. Additionally we did not document an association between early life infection, perinatal characteristics or stressful life events and JIA in this study. The association between premature delivery suggested by our data needs to be further studied in additional JIA cohorts.

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Abbreviations

JIA	Juvenile Idiopathic Arthritis
OR	Odds Ratio
CI	Confidence Interval
RF	Rheumatoid factor

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Significance and Innovations

- The study provides the first data from Northern America regarding varying environmental and early life exposures and their association with JIA.
- Data from this study suggest that there is likely no association between prenatal smoking or possibly secondhand smoking and JIA. Unlike adult data lack of smoking association with JIA seems plausible as most JIA is not seropositive (rheumatoid factor or anti-cyclic citrullinated peptide).
- The study demonstrates no association between JIA and breastfeeding, hospitalization with infection in first year of life, daycare attendance before 6 years of age, household pets or residential area.
- The increased association with premature delivery noted in this study needs to be evaluated in further studies.

Table 1

Demographic characteristics of juvenile idiopathic arthritis (JIA) cases and playmate-matched controls.*

	Playmate-matched Control** (n=138)	Case** (n=225)
Female	78 (56.5)	159 (70.7)
Age at time of survey (years) mean (sd, IQR)	10.7 (4.1, 8 – 14)	11.1 (4.1, 8 – 15)
Duration of diagnosis (years) mean (sd, IQR)		5.1 (3.7, 2–7.5)
Race		
Caucasian	110 (79.7)	191 (84.9)
Other (Asian, African-American, Native American)	5 (3.6)	18 (8)
Multiracial	18 (13)	16 (7.1)
Ethnicity		
Hispanic or Latino	11 (8)	22 (9.8)
Annual household income ($/year)		
< 25,000	4 (2.9)	15 (6.7)
25,000–49,999	11 (8)	31 (13.8)
50,000–74,999	29 (21)	43 (19.1)
75,000–99,999	24 (17.4)	26 (11.6)
100,000–150,000	26 (18.8)	52 (23.1)
>150,000	26 (18.8)	32 (14.2)
Perinatal Characteristics		
Birth Weight (grams)		
Low (<2500)	7 (5.1)	14 (6.2)
Normal (2500–3999)	94 (68.1)	166 (73.8)
High (≥4000)	24 (17.4)	31 (13.8)
Mode of delivery		
Vaginal	89 (64.5)	147 (65.3)
C-section	44 (31.9)	57 (25.3)
Forceps/ Vacuum	1 (0.7)	14 (6.2)
Gestational age (weeks)		
Pre-term (< 37)	11 (8)	32 (14.2)
Term (37–41)	88 (63.8)	151 (67.1)
Post-term (≥42)	22 (15.9)	32 (14.2)
Place of delivery		
Hospital or Birthing Center	120 (87)	185 (82.2)
Home	0 (0)	5 (2.2)
Body Mass Index (kg/m^2)		
Underweight (<18.5)	50 (36.2)	97 (43.1)
Normal (18.5–<25)	54 (39.1)	90 (40)
Overweight (25–<30)	6 (4.3)	24 (10.7)
Obese (≥ 30)	3 (2.2)	12 (5.3)
Smoking		
Household Smoking	25 (18.1)	41 (18.2)

	Playmate-matched Control** (n=138)	Case** (n=225)
Maternal prenatal smoking	6 (4.3)	11 (4.9)
1–9 cigarettes/day	2 (1.4)	7 (3.1)
10–19 cigarettes/day	3 (2.2)	3 (1.3)
20+ cigarettes/day	0 (0)	1 (0.4)
Duration prenatal smoking (months)	(n=5)	(n=8)
mean (sd)	7.2 (3.0)	5.3 (3.0)
median (IQR)	9 (5, 9)	5 (3, 8)
Maternal smoking	9 (6.5)	25 (11.1)
Smoked inside house	2 (1.4)	1 (0.4)
Smoked outside house	7 (5.1)	24 (10.7)
1–9 cigarettes/day	0 (0)	8 (3.6)
10–19 cigarettes/day	3 (2.2)	9 (4)
20+ cigarettes/day	3 (2.2)	4 (1.8)
Paternal smoking	17 (12.3)	26 (11.6)
Smoked inside house	2 (1.4)	2 (0.9)
Smoked outside house	15 (10.9)	24 (10.7)
1–9 cigarettes/day	5 (3.6)	9 (4)
10–19 cigarettes/day	3 (2.2)	5 (2.2)
20+ cigarettes/day	5 (3.6)	7 (3.1)
Relative smoking	6 (4.3)	13 (5.8)
Smoked inside house	1 (0.7)	1 (0.4)
Smoked outside house	5 (3.6)	12 (5.3)
1–9 cigarettes/day	4 (2.9)	5 (2.2)
10–19 cigarettes/day	0 (0)	1 (0.4)
20+ cigarettes/day	1 (0.7)	1 (0.4)
Breastfed	112 (81.2)	184 (81.8)
Duration of breastfeeding (months)		
<6	26 (18.8)	47 (20.9)
6–12	29 (21)	53 (23.6)
12 – 24	48 (34.8)	57 (25.3)
≥24	5 (3.6)	16 (7.1)
Cow's milk introduction ***		
< 1 year of age	11 (8)	30 (13.3)
≥1 year of age	100 (72.5)	176 (78.2)
Early life infections		
Hospitalization for infection <1 year	8 (5.8)	27 (12)
Daycare attendance < 6 years	67 (48.6)	120 (53.3)
Household pets	99 (71.7)	159 (70.7)
Dog	46 (33.3)	63 (28)
Cat	20 (14.5)	38 (16.9)
Other	6 (4.3)	4 (1.8)
More than one pet	27 (19.6)	53 (23.6)

	Playmate-matched Control** (n=138)	Case** (n=225)
At least one dog in the household	73 (52.9)	112 (49.8)
At least one cat in the household	41 (29.7)	87 (38.7)
At least one other type of pet	15 (10.9)	19 (8.4)
Birth Order		
First	59 (42.8)	94 (41.8)
Second	53 (38.4)	83 (36.9)
Third or more	26 (18.8)	45 (20)
Stressors		
None	79 (57.2)	132 (58.7)
Any one stressor	38 (27.5)	58 (25.8)
Multiple stressors	18 (13)	33 (14.7)
Type of stressor		
Death in family	21 (15.2)	17 (7.6)
Divorce in family	5 (3.6)	21 (9.3)
Move in family	23 (16.7)	49 (21.8)
New school	26 (18.8)	38 (16.9)
Unemployment	7 (5.1)	8 (3.6)
Other characteristics		
Maternal age (years)		
<20	0 (0)	2 (0.9)
20–34	49 (35.5)	107 (47.6)
35+	86 (62.3)	111 (49.3)
Paternal age (years)		
<20	1 (0.7)	1 (0.4)
20–34	40 (29)	80 (35.6)
35+	93 (67.4)	126 (56)
Mother's marital status		
Married or Living partner	126 (91.3)	192 (85.3)
Single/Separated/Divorced/Widowed	12 (8.7)	32 (14.2)
Residential area		
Urban	93 (67.4)	135 (60)
Rural	44 (31.9)	87 (38.7)
Moved residence	54 (39.1)	105 (46.7)
Type of residential move		
Urban to Urban	24 (17.4)	49 (21.8)
Urban to Rural	4 (2.9)	10 (4.4)
Rural to Urban	3 (2.2)	8 (3.6)
Rural to Rural	11 (8)	17 (7.6)

*Values are frequency (percentage) unless otherwise indicated.

**Some variables may not add up to totals due to missing data.

***Three JIA cases never introduced cow's milk into diet.

Abbreviations: sd: standard deviation, IQR: interquartile range

Table 2

Risk estimates for environmental/ early life exposures and juvenile idiopathic arthritis (JIA) for playmate-matched (unadjusted and adjusted) controls.

Characteristic	Playmate-matched Unadjusted Odds Ratio (95% CI)	Playmate-matched Adjusted* Odds Ratio (95% CI)
Female	1.75 (1.14, 2.69)	1.80 (1.25, 2.59)
Race		
Caucasian	reference	
Other (Asian, African-American, Native American)	2.10 (1.18, 3.76)	1.19 (0.51, 2.75)
Multiracial	0.51 (0.39, 0.68)	0.42 (0.30, 0.58)
Ethnicity		
Not Hispanic or Latino	reference	
Hispanic or Latino	1.14 (0.72, 1.81)	1.39 (0.88, 2.18)
Annual household income ($/ year)		
< 25,000	2.70 (0.59,12.41)	
25,000–49,999	1.90 (0.84, 4.29)	
50,000–74,999	reference (median annual household income)	
75,000–99,999	0.77 (0.35, 1.67)	
100,000 –150,000	1.43 (0.99, 2.06)	
>150,000	0.89 (0.58, 1.37)	
Perinatal Characteristics		
Birth weight (grams)		
Low (<2500)	1.16 (0.53, 2.56)	1.21 (0.51, 2.87)
Normal (2500–3999)	reference	
High (≥4000)	0.73 (0.39, 1.37)	0.72 (0.36, 1.47)
Mode of delivery		
Vaginal	reference	
C-section	0.83 (0.46, 1.51)	1.08 (0.54, 2.14)
Forceps/ vacuum	8.40 (3.52, 20.05)	6.29 (2.77,14.27)
Gestational age (weeks)		
Pre-term (< 37)	1.81 (1.23, 2.65)	1.80 (1.22, 2.66)
Term (37–41)	reference	
Post-term(≥42)	0.81 (0.41, 1.59)	0.73 (0.37, 1.47)
Body Mass Index (kg/m^2)		
Underweight (<18.5)	1.17 (0.50, 2.76)	1.33 (0.54, 3.24)
Normal (18.5–<25)	reference	
Overweight (25–<30)	2.16 (0.71, 6.59)	1.44 (0.33, 6.32)
Obese (≥30)	2.53 (0.53,12.14)	3.89 (1.82, 8.34)
Cigarette smoke exposure		
Household smoking	0.94 (0.67, 1.31)	0.82 (0.49, 1.37)
Maternal prenatal smoking	1.07 (0.45, 2.55)	0.82 (0.25, 2.67)
Quantity smoked (cigs/day)		

Characteristic	Playmate-matched Unadjusted Odds Ratio (95% CI)	Playmate-matched Adjusted* Odds Ratio (95% CI)
Non-smokers	reference	
1–9	2.01 (0.49, 8.34)	1.71 (0.34, 9.15)
10+	0.86 (0.24, 3.04)	0.59 (0.10, 3.30)
Duration smoking (months)	0.99 (0.59, 1.64)	Does not converge
Maternal smoking	1.65 (0.74, 3.68)	1.75 (0.49, 6.30)
Smoked inside house	0.33(0.02, 5.02)	0.14 (0.01, 1.66)
Smoked outside house	2.04 (1.03, 4.05)	2.14 (0.56, 8.14)
Quantity smoked (cigs/day)		
Non-smokers	reference	
1–19	3.17 (1.61, 9.44)	2.43 (0.70, 8.43)
20+	0.83 (0.12, 5.93)	1.01 (0.10, 10)
Paternal smoking	0.91 (0.60, 1.40)	0.82 (0.43, 1.60)
Smoked inside house	0.67 (0.12, 3.83)	0.64 (0.45, 0.92)
Smoked outside house	0.95 (0.55, 1.64)	0.85 (0.43, 1.67)
Quantity smoked (cigs/day)		
Non-smokers	reference	
1–9	1.09 (0.35, 3.35)	0.88 (0.28, 2.73)
10–19	0.94 (0.18, 5.00)	0.79 (0.16, 3.99)
20+	0.82 (0.42, 1.61)	0.88 (0.25, 3.15)
Relative smoking	1.27 (0.28, 5.69)	1.12 (0.19, 6.55)
Smoked inside house	0.75 (0.04, 14.73)	0.26 (0.01, 5.75)
Smoked outside house	1.37 (0.33, 5.73)	1.38 (0.24, 8.10)
Quantity smoked (cigs/day)		
Non-smokers	reference	
1–9	0.66 (0.07, 6.08)	0.56 (0.07, 4.34)
10+	1.34 (0.11,16.45)	0.63 (0.05, 8.36)
Breastfed		
Yes	reference	
No	0.96 (0.76, 1.22)	0.85 (0.65, 1.10)
Duration breastfed (months)		
Not breastfed	0.88 (0.62, 1.25)	0.76 (0.48, 1.19)
<6	0.94 (0.54, 1.64)	0.75 (0.39, 1.46)
6–12	reference	
12 – 23	0.67 (0.32, 1.43)	0.74 (0.33, 1.65)
≥24	1.91 (0.82, 4.43)	2.23 (0.94, 5.31)
Cow's milk introduction		
≥1 year of age	reference	
< 1 year of age	1.57 (0.91, 2.70)	1.45 (0.74, 2.84)
Early life infections	2.25 (0.96, 5.28)	2.12 (0.81, 5.55)
Hospitalization for infection < 1 year	1.22 (0.80, 1.88)	1.06 (0.64, 1.76)
Daycare attendance < 6 years		

Characteristic	Playmate-matched Unadjusted Odds Ratio (95% CI)	Playmate-matched Adjusted* Odds Ratio (95% CI)
Birth Order		
First	reference	
Second	0.97 (0.59, 1.59)	0.86 (0.49, 1.52)
Third or more	1.07 (0.58, 1.96)	0.87 (0.48, 1.57)
Household pets	no pets (reference)	
At least one pet	0.98 (0.68, 1.41)	1.19 (0.74, 1.92)
Dogs only	0.81 (0.48, 1.36)	1.06 (0.58, 1.92)
Cats only	1.18 (0.79, 1.77)	1.31 (0.81, 2.13)
Other pets only	0.36 (0.21, 0.64)	0.40 (0.22, 0.76)
More than one type of pet	1.16 (0.77, 1.74)	1.51 (0.83, 2.73)
At least one dog Ref: no dog	0.88 (0.59, 1.31)	1.08 (0.64, 1.83)
At least one cat Ref: no cat	1.55 (0.98, 2.44)	1.67 (1.04, 2.68)
At least one other pet Ref: no other pet	0.77 (0.41, 1.44)	0.90 (0.44, 1.83)
Stressors		
No stressors	reference	
Any one stressor	0.86 (0.64, 1.17)	0.83 (0.52, 1.33)
Multiple stressors	0.94 (0.53, 1.66)	0.65 (0.43, 1.00)
Type of stressor	0.42 (0.19, 0.92)	0.31 (0.11, 0.87)
Death in family Ref: no death	2.47 (0.95, 6.39)	1.57 (0.60, 4.12)
Divorce in family Ref: no divorce	1.27 (1.00, 1.61)	1.20 (0.85, 1.71)
Move in family Ref: no move	0.89 (0.55, 1.46)	0.85 (0.44, 1.64)
New school Ref: no new school	0.60 (0.37, 0.97)	0.23 (0.09, 0.59)
Unemployment Ref: no unemployment		
Other risk estimates		
Maternal age (years)		
20–34	reference	
35+	0.62 (0.34, 1.11)	0.59 (0.34, 1.01)
Paternal age (years)		
20–34	reference	
35+	0.70 (0.36, 1.34)	0.72 (0.43, 1.20)
Mother's marital status		
Married or Living partner		reference
Single/Separated/Divorced/ Widowed	1.62 (0.71, 3.70)	0.89 (0.29, 2.71)
Residential area		
Urban	reference	
Rural	1.25 (0.84, 1.87)	1.19 (0.79, 1.77)
Moved residence	1.25 (0.72, 2.16)	1.35 (0.97, 1.88)
Type of residential move		
Urban to Urban	reference	
Urban to Rural	1.54 (0.43, 5.60)	2.29 (0.54, 9.68)
Rural to Urban	1.22 (0.29, 5.12)	1.35 (0.40, 4.62)

Characteristic	Playmate-matched Unadjusted Odds Ratio (95% CI)	Playmate-matched Adjusted* Odds Ratio (95% CI)
Rural to Rural	0.58 (0.16, 2.12)	0.73 (0.22, 2.40)

*Adjusted for age at time of survey and annual household income

Abbreviations: CI; confidence interval, cigs; cigarettes, Ref; reference