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Characteristics of Children with Asthma Who Achieved Remission of Asthma

Asma Javed, M.B.B.S.¹, Kwang Ha Yoo, M.D., PH.D.^{1,2}, Kanishtha Agarwal, M.D., M.P.H.¹, Robert M. Jacobson, M.D.¹, Xujian Li, M.S.³, and Young J. Juhn, M.D., M.P.H.^{1,*}

¹Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA.

²Department of Internal Medicine, Konkuk University College of Medicine, Seoul, South Korea.

³Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA.

Abstract

Objective—To characterize two groups of asthmatics who had achieved remission and those who had not achieved remission of asthma.

Methods—The study was a retrospective cohort study based on 117 asthmatic children who participated in a previous study. We categorized the children into two groups: asthmatics with remission versus asthmatics without remission. We defined remission of asthma as lack of symptoms/signs of asthma or asthma-related medications or health care services for at least three consecutive years. Long-term remission was defined by no relapse of asthma after achieving remission. We characterized these groups.

Results—Of the 117 subjects, 70 (60%) were male, 91 (78%) were Caucasians, and the mean age at index date of asthma was 8.1 years. A total of 59 asthmatic children (50%) achieved remission and 28 asthmatics (24%) achieved long-term remission. Asthmatics with remission were more likely to be Caucasian (87%) compared to those without (69%) ($p = .039$). There were no differences in the frequency of visits for viral (0.3 vs. 0.4 per person-years, $p = .29$) or bacterial infections (0.7 vs. 0.5 per person-years, $p = .49$) between asthmatics with and without remission. Gender, socioeconomic status, smoking exposure, family history of asthma or atopy, breastfeeding history, peak flow meter availability, asthma action plan, and influenza vaccinations were not associated with remission.

Conclusions—Only half of asthmatic children accomplished remission of asthma ever and 24% of asthmatic children had long-term remission. Ethnicity may affect remission of asthma but microbial infections may not influence the likelihood of remission of asthma and vice versa.

Keywords

asthma; childhood; epidemiology; microbial infection; remission; risk

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*Corresponding author: Young J. Juhn, M.D., M.P.H., Division of Community Pediatric and Adolescent Medicine, Department of Pediatric and Adolescent Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; Tel: 507-538-6522; Fax: 507-284-9744; juhn.young@mayo.edu.

Declaration of Interest

The study investigators have nothing to disclose that poses a conflict of interest.

Introduction

Asthma is the most common chronic illness in childhood and is a major cause of morbidity in adults, affecting 4–17% of children and 7.7% of adults in the United States (1–3), comprising of nearly 30 million Americans and 300 million people globally (4). At present, there are no overall signs of a declining trend in asthma prevalence; rather, asthma continues to increase in many parts of the world (3,5,6). The total incremental cost of asthma to society is estimated to be \$56 billion in the United States (2) and the mean total cost per patient ranged from EUR 509 (controlled asthma) to EUR 2281 (uncontrolled disease) suggesting that asthma, especially poorly controlled asthma, is a significant medical and economic burden to society (7). Achieving remission of asthma might result in significant cost savings for asthma care and understanding of remission of asthma might help us accomplish this goal.

Despite new treatment options and guidelines, controlling asthma symptoms is still a significant challenge. A previous study based on the Asthma Care Network reported that more than 60,000 patients from 2876 practice sites (68% of pediatric patients and 78% of adult patients) had limited activities due to asthma in the past week; 62% of pediatric patients and 68% of adult patients reported more than 2 days with asthma symptoms in the past week (8). Thus, a significant proportion of patients with asthma do not achieve remission of asthma, whereas some asthmatics still achieve remission. Previous studies assessing the proportions of children who achieved remission of asthma showed widely varying remission rates ranging from 20–65% (see Table 1 for the literature summary on remission of asthma) (9–17). For example, the most recent study by Burgess et al. (Tasmanian Longitudinal Health Study) defined remission as not having had an asthma attack for 2 years and not using current asthma medication, or no self-reported asthma in adult life but with parent-reported childhood asthma during survey (10). The study reported that 65% of patients achieved remission. While self-reported health outcomes are important, studying remission status of asthma and its associated factors based on medical record provides additional information and addresses some limitations of self-reported outcome measures (18–21). There are few reports in the literature that assessed remission status of asthma and factors associated with remission based on clinician's reported history as well as health care services documented in medical records. In addition, the duration of remission of asthma among children with asthma during their first 18 years of life since onset of asthma is unknown. Also, there are few studies examining the role of remission in the frequency of clinically significant viral or bacterial infections and vice versa.

We conducted a retrospective cohort study to determine the proportion of children who achieved remission of asthma and the duration of remission of asthma during the first 18 years of life among children with asthma. As a secondary aim, we characterized asthmatics who achieved remission.

Methods

This study was approved by the Institutional Review Boards at both Mayo Clinic and the Olmsted Medical Center.

Study Setting

Characteristics of Olmsted County populations were similar to those of the US Caucasian population with the exception of a higher proportion of the working population employed in the health care industry (22–24). Olmsted County, MN, is an excellent setting to conduct an epidemiologic study such as this because medical care is virtually self-contained within the community. Under the auspices of the Rochester Epidemiology Project (REP) (25), each

patient is assigned a unique identifier; all clinical diagnoses and visits are electronically indexed, and information from every episode of care is contained within detailed patient-based medical records. Using REP resources, we previously demonstrated that incidence rates of asthma for this community are similar to other communities. For example, the incidence rate of asthma in Rochester was 238 cases per 100,000 persons, which is comparable to those in other communities such as Tecumseh, MI (250/100,000) during the study period (26).

Study Design and Subjects

The details of the study subjects and methods were previously reported (27,28). Briefly, the study was designed as a retrospective cohort study following children with asthma during the first 18 years of life since onset of asthma when one met the criteria for asthma in Table 2. We determined the proportion of children who had achieved remission of asthma and the total duration of remission. Also, we characterized those who achieved remission. Study subjects included 342 healthy children consisting of a population-based stratified sample (aged 12–18 years) who participated in a previous study. Of these 342 children, 117 children met the criteria for asthma and were eligible for the present study. We excluded subjects who did not grant research authorization for medical record review or who were not Olmsted County residents.

Determination of Asthma

We conducted comprehensive medical record reviews to apply predetermined criteria for asthma (Table 2). The criteria for asthma based on medical record review were originally developed during a previous study by Yunginger and Reed et al. (24) To assess the reliability of the criteria, random samples of records were reviewed by different nurse abstractors and analyzed for interobserver reliability; agreement rates between abstractors and a high degree of concordance were found (29). These criteria have been extensively used in research for asthma epidemiology (24,29–37). We included both definite and probable asthma, as most probable asthmatics become definite over time (24,38). Each asthmatic child had an index date of asthma, which was defined by the time when one met the criteria for asthma. Asthma status, as defined above, was determined first. Subsequently, we determined the specific asthma index date and asthma diagnosis date. We defined the asthma index date as the earliest constellation of symptoms (including cough, dyspnea, and/or wheeze) found in the medical record which met the predetermined criteria for asthma in Table 2.

Remission of Asthma

The literature suggests different definitions for remission of asthma based on duration ranging from 1–6 years (9–17). In addition, there is considerable variation in the determination of remission with some studies based on resolution of clinical symptoms (9–11,13,14,17), while others have required objective measure of normal lung function (12,14–16). Since there is no consensus to define remission of asthma and defining remission of asthma is not the scope of this present work, we followed the definition of remission by the Melbourne Epidemiological Study of Childhood, which is the longest and most comprehensive longitudinal study of childhood asthma (39). In our study, remission of asthma was defined by lack of symptoms/signs of asthma for at least three consecutive years without (1) asthma symptoms/signs according to clinician's medical record; (2) patient's use of asthma medications; (3) clinic, urgent care, or emergency department (ED) visits for asthma symptoms; and (4) hospitalization for asthma. Relapse is defined by the occurrence of any of these events for asthma. According to these criteria, we dichotomized subjects into two groups: (1) asthmatics who achieved remission and (2) those who had never achieved remission. Asthmatics who achieved remission included two groups of children: children

with short-term remission and long-term remission. We defined long-term remission as no recurrence or relapse of symptoms of asthma after achieving remission until last follow-up date or 18th birthday, whichever occurred first. Short-term remission was defined as recurrence or relapse of asthma symptoms/signs after achieving remission. We determined the specific dates for the duration of remission when one met the criteria for remission to calculate the total duration of remission (not necessarily consecutive).

Factors Associated with Remission

Variables were collected, which included sociodemographic (age, gender, ethnicity, and educational status), exposure to cigarette smoking at the time of index date of asthma, family history of asthma or atopy, breastfeeding history, all clinic visits (urgent care or ED for viral infections or bacterial infections based on a physician diagnosis documented in medical record), peak flow meter availability, asthma action plan, and influenza vaccinations. Since asthma medication use is one of the criteria for remission of asthma, we did not assess the role of asthma medications in remission.

Statistical Analyses

The primary analysis was to determine the proportion of children with asthma who achieved remission, duration of remission, and factors associated with remission. Subjects were followed from their asthma index date to the date of remission of asthma during their first 18 years of age. Subjects were dichotomized into two groups: (1) those achieving remission and (2) those not achieving remission. For those who achieved remission, we determined the proportions of asthmatics who achieved long-term remission defined by no relapse or recurrence of asthma symptoms after achieving remission and those with short-term remission defined by the achievement of remission but relapse of asthma symptoms. In addition, we calculated the total duration of remission after one met the criteria for remission described above. If relapse occurred intermittently, we summed up all durations of remission during the first 18 years of life.

We compared sociodemographic and clinical variables between the two groups of asthmatics as discussed above by using logistic regression models adjusting for the follow-up period from index date of asthma to the last visit day or 18th birthday whichever comes first. The frequency of all visits (clinic, urgent care, and ED) for viral or bacterial infections were calculated as incidence density rate (number of episode per person-years) from index date of asthma to the last follow-up date or 18th birthday, whichever comes first. Associations were summarized by calculating odds ratios (ORs) and corresponding 95% CI. In this study, because of a relatively small sample size in categories of each variable, we did not run a multivariate model. All calculated *p*-values were two-sided, and *p*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS software package (SAS version 8.2; SAS Institute Inc, Cary, NC, USA).

Results

Study Subjects

The characteristics of the subjects and the relationship between individual risk factors and asthma remission are summarized in Table 3. Of the 117 subjects, 70 (60%) were male and 91 (78%) were Caucasian. The mean age of asthmatics at index date was 8.1 years (standard deviation 5.0). There were 32 subjects who had been on inhaled corticosteroid (single or combination) therapies during the follow-up period from index date of asthma to the last follow-up date or 18th birthday, whichever occurred first. Of the 117 asthmatics who met the criteria for asthma, 27 (23%) asthmatics did not have a physician diagnosis of asthma in medical records during the study period, suggesting a delayed diagnosis of asthma.

Remission of Asthma

Of the eligible 117 subjects who met the criteria for asthma, 59 subjects (50%) were asthmatics with remission; 58 were asthmatics without remission. Out of the 59 asthmatics with remission, 28 (24%, 28/117) achieved long-term remission. The remaining 31 patients achieved remission but relapsed before last follow-up date or 18th birthday (i.e., short-term remission). The mean duration of remission among asthmatics who achieved remission was 6.9 years with a standard deviation of 3.8 during 11.2 years of the mean follow-up period. The mean duration of remission among asthmatics with long-term remission was 7.4 years with a standard deviation of 4.6 during 8.9 years of the mean follow-up period.

Factors Associated with Remission

The results on the comparison between asthmatics with or without remission are summarized in Table 3. Asthmatics with remission were more likely to be Caucasian (87%) compared with those without remission (69%) ($p = .039$). The frequency of all visits for viral infections from index date of asthma to last follow-up date or 18th birthday, whichever comes first, did not differ between asthmatics with remission (0.57 per person-years, 95% CI: 0.52–0.63) and those without remission (0.54 per person-years, 95% CI: 0.47–0.61) ($p = .70$). Similarly, asthmatics with remission had comparable rates of bacterial infections to those without remission (0.84 person-years, 95% CI 0.78–0.92 vs. 0.73 person-years, 95% CI: 0.66–0.83, $p = .40$). Gender, socioeconomic status, smoking exposure, family history of asthma or atopy, breastfeeding history, peak flow meter availability, asthma action plan, and influenza vaccinations were not associated with remission of asthma.

Discussion

Our study results suggest that 50% of children with asthma achieved remission during their first 18 years of life (24% for long-term remission) based on medical record. The mean duration of remission was approximately 6.9 years (± 3.8 years) of a 10-year follow-up. Ethnicity is an important factor associated with remission. Microbial infections which required medical evaluations did not affect the likelihood of remission and vice versa.

To date, assessment of remission rate and duration of asthma has not been performed based on comprehensive medical record reviews in a self-contained health care environment during the first 18 years of life among children with asthma. Despite the difference in the study design, remission rates of asthma in our study appear to be within the reported range of remission rate of asthma, although it varies widely (20–65%) (9–17,39–41). The Melbourne Epidemiological Study of Childhood Asthma is the lengthiest and most comprehensive longitudinal study of childhood asthma (39). It is similar to the current study in terms of definition of remission (3 years). Children between the ages of 7 and 10 years were recruited and followed up every 7 years until the age of 42 years. At last follow-up, 85% of the control group, 60% of those with episodic asthma, and 21% of those with persistent or severe asthma at recruitment had been free of wheezing over the previous 3 years. The most recent study published by Burgess et al. is a population-based cohort study (Tasmanian Longitudinal Health Study) in which the main outcome measure was asthma remission defined as no asthma attack for 2 years and no current asthma medication use or self-reported asthma in adult life but with parent-reported childhood asthma (10). The results showed asthma remission rate being 65%. History of allergic rhinitis and/or eczema was negatively associated with remission.

None of the previous studies determined the specific duration of asthma remission based on medical record reviews. Thus, we could not compare our results with the literature. From the mean age at the time of index date of asthma (8.1 years), 24% of children with asthma

achieved long-term remission (i.e., no relapse after remission) with a duration of 7.4 years (± 4.6) before the last follow-up date or their 18th birthday (their mean follow-up duration was 8.9 years), whereas those who achieved short-term remission (i.e., multiple relapses after remissions) had a collective duration of 6.9 years of remission (± 3.8) (their mean follow-up duration was 13.3 years). Considering the follow-up duration and only 24% of asthmatics with long-term remission in our study, these data suggest that even if children with asthma had ever achieved remission, they still tend to experience frequent relapses of asthma intermittently throughout the first 18 years of life since index date of asthma. Our study is limited in answering why some asthmatics have a longer duration of remission, others not due to a small sample size. However, Caucasian children with asthma were more likely to achieve remission compared with non-Caucasian children. The literature suggests that non-Caucasian children tend to have more severe asthma in addition to poor asthma control (42–45). For other factors associated with remission of asthma, atopic conditions other than asthma have been reported to be associated with remission of asthma (10,46), but in our study it only approached statistical significance. In contrast with the reported role of respiratory infections in development and acute exacerbation of asthma (47–50), our study did not reveal that the frequency of clinically significant microbial infections (frequency of clinic, urgent care, and ED visits for upper respiratory infections) was not associated with remission of asthma during the first 18 years of life. These results suggest that the duration of remission of asthma might not influence the likelihood of viral or bacterial respiratory infections, nor might such respiratory infections affect the likelihood of remission of asthma. A previous international prospective study supported this study finding (12). In addressing the study aim of the association between respiratory infections and the likelihood of remission of asthma, our study may be limited because it may not capture all respiratory infections since it was based on medical record review. However, our previous study showed that the frequency of microbial infections reflected in medical record (i.e., the number of clinic visits for infections) was highly correlated with the frequency of symptomatic microbial infections which children experienced (51). Thus, the lack of the association between frequency of respiratory infections and remission of asthma may suggest the following: the role of respiratory infections in exacerbation or control of asthma might become less influential as children become older as the frequency of respiratory infections decrease as children age (52,53) and viral illness-induced wheezing episodes may be developmental (age-dependent) (54). Further studies are needed to assess the long-term impact of microbial infections on remission of asthma.

The main strength of the present study includes epidemiologic advantages consisting of self-contained health care environment and unified medical record system for research among health care providers in the community. Asthma was ascertained by predetermined criteria and remission was based on comprehensive medical record review, which captured all asthma-related health care services. This is another strength of the study. This study is the first to determine remission of asthma based on health care services documented in medical record rather than patient or parents' self-report. Our study has inherent limitations as a retrospective study. Some variables (e.g., pulmonary function test results or atopic sensitization) were unavailable. Also, since remission of asthma was based on health care services documented in the medical record, all asthma symptoms or asthma-related events may not have been captured. Thus, our study may overestimate the remission rate of asthma, although the result was within the range of remission rates reported by the literature. Our study did not examine the role of asthma medications in remission of asthma due to the criteria for remission. Our study results were based on a small sample size and Caucasian population, which may limit generalizability of our study findings.

In conclusion, only half of asthmatic children accomplished remission of asthma and 24% of asthmatic children had long-term remission. Ethnicity may influence remission of asthma,

but microbial infections may not influence the likelihood of remission status and vice versa. Regarding the assessment of remission, health care service data should be supplementary to self-reported data.

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TABLE 1

Summary of the literature on remission of asthma.

Author	Study design	Sample size and follow-up duration	Definition of asthma	Definition of remission	% of remission	Strength	Limitations
De Marco et al. (11)	Cross-sectional survey	<i>n</i> = 18,873 (0–44 years)	Self-report via screening questionnaire-	2 years of absence of symptoms, 1 year without asthma medications	45.8%	Large population-based study	Relies on patient recall
Bronniman et al. (9)	Prospective study	<i>n</i> = 3454 on initial survey, 2300 completed second survey	Self-report via questionnaire at two points in time 8 years apart	Lack of “active” symptoms of asthma	22%	–Multistage stratified cluster sample of 1655 households– Correlation with spirometry results	–Mainly Caucasian population–Relies on patient recall–Significant transfer bias
Burgess et al. (10)	Population-based cohort study	<i>n</i> = 1811 7-year-old Tasmanian school-children who were re-surveyed in 2004.	Self-report via questionnaire	No asthma attack for 2 years and no current asthma medication use, or no self-reported asthma in adult life but with parent-reported childhood asthma.	65%	Longitudinal data gathered over 40 years small loss to follow-up.	–Relies on parental recall of their child’s asthma (“clinical remission”)
Martin et al. (14)	Random sample studied prospectively	<i>n</i> = 295 ‘asthmatic’ children 105 controls at initial cohort at age 7 followed till 21 years of age	Self-report via questionnaire	Asthma symptoms or contact with physicians for asthma	55% of those whose wheezing started before 7 years.	Prospective study of a random cohort	–Significant loss to follow-up
To et al. (17)	Longitudinal population-based cohort study.	<i>n</i> = 34,216 aged <6 years, followed until 11 years	1 asthma hospitalization or 2 asthma physician claims within 3 years prior to age 6 years	No hospitalization and/or physician visit during entire follow-up period	48.6%	Remission definition was not self-report but hospitalization and clinic visit	–Diagnosis of asthma on 2 physician claims in 2 years, disease – Misclassification of asthma—Use of asthma medication not factored in
Sears et al. (15)	Longitudinal, population-based, cohort study	<i>n</i> = 1139 born between 1972 and 1973	Any wheezing symptoms	Absence of wheezing after wheezing had been reported at two or more successive prior assessments	27.4%	Recall bias due to self-report via questionnaire	– Recall bias due to self-report via questionnaire —Assessing outcomes relatively early in adult life may overestimate the number of remissions and underestimate the number of relapses
Holm et al. (13)	Longitudinal prospective study	<i>n</i> = 1153 individuals	Self-report of asthma	Remission was defined as no asthmatic	20.2 per 1000 person-years	Prospective study	Recall bias due to self-report via questionnaire

Author	Study design	Sample size and follow-up duration	Definition of asthma	Definition of remission	% of remission	Strength	Limitations
		(aged 26–53 years)		symptoms in two consecutive years and no current use of asthma medication.			
Kjellman et al. (44)	Prospective study	$n = 160$ 3–18 years	Three or more episodes of wheezing were used for a diagnosis of asthma	Free from asthma symptoms and medication during the year prior to the last follow-up.	16%	Prospective study	–A small sample size and questionnaire-based asthma ascertainment— Self-report for remission
Taylor et al. (16)	Longitudinal study of birth cohort ($n = 1037$) born in New Zealand in 1972–1973.	($n = 1037$) Age 3 onward, prospectively followed Participants of age), and allergen skin-prick testing (13 years and 21 years of age).	Self-report via questionnaire as well as pulmonary function tests	At 18 years of age, absence of reported wheezing that had been current at two or more prior assessments	40%	Longitudinal study, continues until 26 years of age	–Self-report for remission

TABLE 2

Criteria for asthma.

Patients were considered to have definite asthma if a physician had made a diagnosis of asthma or if each of the following three conditions were present (see list below). Patients were considered to have probable asthma if the first two of the following three conditions were present:

1. History of cough with dyspnea and/or wheezing or history of cough and/or dyspnea plus wheezing on examination
2. Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent
3. Two or more of the following:

Sleep disturbance by nocturnal cough and wheeze

Nasal polyps

Blood eosinophilia higher than 300/uL

Positive wheal and flare skin tests or elevated serum IgE

History of hay fever or infantile eczema or cough, dyspnea, and wheezing regularly on exposure to an antigen

Pulmonary function tests showing one Forced Expiratory Volume one second (FEV₁)^a or Forced Vital Capacity (FVC)^b <70% predicted and another with at least 20% improvement to an FEV₁^a of higher than 70% predicted or methacholine challenge test showing 20% decline in FEV₁^a

Favorable clinical response to bronchodilator

Patients were excluded from the study if any of these conditions are present:

Pulmonary function tests that showed FEV₁^a to be consistently below 50% predicted or diminished diffusion capacity

Tracheobronchial foreign body at or about the incidence date

Hypogammaglobulinemia (IgG less than 2.0 mg/mL) or other immunodeficiency disorder

Wheezing occurring only in response to anesthesia or medications

Bullous emphysema or pulmonary fibrosis on chest radiograph

PiZZ α 1-antitrypsin

Cystic fibrosis

Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

TABLE 3

Characteristics of asthmatics with vs. without remission (factors associated with remission).

Variables	Remission (n = 59)	No remission (n = 58)	Adj. OR ^a (95% CI)*	p-value*
Follow-up time (years), mean (SD)	11.2 (5.09)	8.4 (4.59)		0.0026
Age at index date of asthma in years	6.7 (5.00)	9.5 (4.71)	0.89 (0.46–1.70)	0.72
Gender (male)	36 (51%)	34 (58.6%)	0.93 (0.43–2.03)	0.86
Ethnicity				
White	51 (86.4%)	40 (69%)	2.73 (1.05–7.09)	0.039
Non-white	8 (13.6%)	18 (31%)	–	
Family history of asthma				
Yes	16 (27.1%)	19 (32.8%)	1.15 (0.48–2.73)	0.76
No	36 (61%)	33 (56.9%)	–	
Maternal education levels in years, mean (SD) ^b	14.3 (1.79)	15 (1.89)	0.86 (0.64–1.15)	0.31
Smoking status				
Yes	9 (19.6%)	9 (18.4%)	1.15 (0.39–3.33)	0.80
No	37 (80.4%)	40 (81.6%)	–	
Freq. of influenza vaccination per person-years, mean (SD) ^b	0.1 (0.19)	0.1 (0.23)	0.91 (0.15–5.52)	0.91
Asthma action plan availability				
Yes	5 (9.6%)	7 (12.7%)	0.70 (0.20–2.43)	0.58
No	47 (90.4%)	48 (87.3%)	–	
Peak flow meter availability				
Yes	18 (34.6%)	24 (43.6%)	0.62 (0.27–1.39)	0.24
No	34 (65.4%)	31 (56.4%)	–	
Family history of atopy				
Yes	16 (27.1%)	19 (32.8%)	0.79 (0.34–1.83)	0.58
No	36 (61%)	33 (56.9%)	–	
Other atopic conditions				
Yes	29 (50.9%)	34 (59.6%)	0.53 (0.24–1.18)	0.12
No	28 (49.1%)	23 (40.4%)		
Breast feeding duration in months, mean (SD) ^b			1.01 (0.84–1.20)	0.95
	3.1 (2.31)	3.3 (2.47)		
Weight at birth, mean (SD) ^b	3521.0 (619.98)	3542.7 (603.23)	1.0 (0.99–1.01)	0.57
Gestational age, mean (SD) ^b	39.2 (2.26)	39.1 (1.90)		0.33
Freq. of viral infections per person-years, Median (interquartile range)	0.3 (0.2–0.8)	0.4 (0.1–0.7)	0.60 (0.23–1.56)	0.29
Frequency of bacterial infections per person-years, Median (interquartile range)	0.5 (0.2–1.0)	0.5 (0.2–0.9)	0.94 (0.74–1.19)	0.49

Notes:

^aOR, odds ratio.

^bSD, standard deviation.