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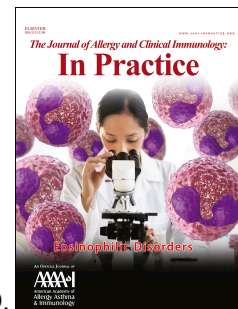
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Abbreviations:

AAP, American Academy of Pediatrics

BMI, body mass index

CDC, the Centers for Disease Control and Prevention

CI, confidence interval

DNA, deoxyribonucleic acid

IgE, immunoglobulin E

IL, interleukin

IPCW, inverse probability censoring weighting method

IPTW, inverse probability treatment weighting method

IQR, interquartile range

OR, odds ratio

RSV, respiratory syncytial virus

T_H1, type 1 T helper cells

T_H2, type 2 T helper cells

WHO, World Health Organization

ABSTRACT

Background: Little is known about the relationship of longitudinal growth trajectory in early life with asthma development, particularly in infants with bronchiolitis (a high-risk population).

Objective: Among infants with bronchiolitis, we aimed to identify growth trajectory profiles and to determine their longitudinal relationship with the risk for developing childhood asthma.

Methods: A multicenter prospective study enrolled infants (aged <1 year) hospitalized for bronchiolitis. We identified growth trajectory profiles—derived from BMI-for-age at ages 0, 6, 12, 15, 18, 24, and 36 months by using a longitudinal clustering method. We examined associations between growth trajectory profiles and asthma development by age 5 years.

Results: The analytic cohort consists of 880 infants hospitalized for bronchiolitis (median age, 3 months). Overall, 26% developed asthma by age 5 years. The longitudinal clustering identified five distinct profiles: persistent low growth (27%), normative growth (33%), transient overweight (21%), late-onset overweight (16%), and persistent obesity (3%) profiles. In multivariable model, compared to children with a normative profile, those with a persistent obesity profile had significantly higher risks of developing asthma (24% vs. 38%, OR 2.55, 95%CI 1.07-6.09, $P=0.03$). Among children with a persistent obesity profile, those without allergic predisposition had significantly higher risks of asthma (OR 3.02, 95%CI 1.05-8.64, $P=0.04$ in the non-parental allergic history group; OR 3.18, 95%CI 1.02-9.92, $P=0.047$ in the non-IgE sensitization group) while those with allergic predisposition were not at increased risk.

Conclusions: This multicenter cohort study of infants with bronchiolitis demonstrated distinct growth trajectory profiles that have differential risks for developing asthma.

Highlights Box**What is already known about this topic?**

Studies suggested associations of aberrant growth trajectories (e.g., persistently-high BMI) with asthma development both in high-risk and general populations. However, little is known about the integrated role of growth trajectory and allergic predisposition in asthma.

What does this article add to our knowledge?

In this prospective cohort of infants hospitalized with-bronchiolitis, the risk of developing asthma was highest in children with persistent obesity profile, particularly in those without allergic predisposition, during the first three years of life.

How does this study impact current management guidelines?

This study suggests the significance of growth trajectory in early life. It may provide evidence for early identification of children at high risk for asthma development and offer opportunities for early targeted prevention interventions.

Keywords: growth trajectory; obesity; body mass index; children; asthma; cohort; allergic predisposition

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Contributors' Statement

Drs. Nanishi, Fujiogi, and Raita carried out the main statistical analysis, drafted the initial manuscript, and approved the final manuscript as submitted. Drs. Stevenson and Qi collected the study data, analyzed and cleaned the data, reviewed and revised the initial manuscript, and approved the final manuscript as submitted. Drs. Liang, Hasegawa, and Camargo conceptualized the study, obtained funding, supervised the statistical analysis, reviewed and revised the initial manuscript, and approved the final manuscript as submitted.

BACKGROUND

Bronchiolitis is the leading cause of hospitalization in American infants, accounting for 110,000 hospitalizations annually.¹ In addition to the substantial acute morbidity, ~30% of infants hospitalized for bronchiolitis subsequently develop asthma.²⁻⁵ Yet, the underlying mechanisms linking these two conditions remain unclear. This major knowledge gap has hindered efforts to prevent asthma in this high-risk population.

In addition to well-described risk factors for asthma development (e.g., allergy, infant bronchiolitis),^{6,7} studies have shown positive association between body mass index (BMI) and risks of adult-onset asthma.⁸⁻¹¹ Likewise, a meta-analysis reported that school-age children with overweight or obesity had a higher risk of incident asthma.¹² Some studies have also shown that birth weight of $\geq 4,500$ grams¹³ and BMI of $\geq 85^{\text{th}}$ percentile during toddlerhood^{14,15} are associated with a higher risk of asthma at an older age. In contrast, others report that a lower, not higher, birth weight¹⁶⁻¹⁸ is associated with a higher risk of respiratory symptoms or asthma and that early life weight gain is not associated with increased risk.¹⁹ Despite the clinical and public health importance, the relationship of longitudinal growth trajectory in early life with asthma development in children—particularly in infants with bronchiolitis (a high-risk population)—remains to be elucidated. Furthermore, while research has suggested the link between obesity and asthma phenotypes (e.g., non-allergic asthma),^{8,10,20,21} little is known about the integrated role of growth trajectory and allergic predisposition (e.g., parental history of asthma, child allergic sensitization) in asthma development.

To address these knowledge gaps, we analyzed data from a prospective cohort study of infants hospitalized with bronchiolitis to 1) identify distinct growth trajectory profiles in the first three years of life by applying longitudinal clustering, 2) determine their relationships with

118 asthma development, and 3) examine whether the association is modified by allergic
119 predisposition.

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METHODS

Study Design, Setting, and Participants

We analyzed data from an ongoing, multicenter, prospective cohort study of infants (aged <12 months) hospitalized for bronchiolitis. This study, called the 35th Multicenter Airway Research Collaboration (MARC-35),²²⁻²⁴ is coordinated by the Emergency Medicine Network (EMNet),²⁵ a research collaboration of 247 participating hospitals.

Using a standardized protocol,²²⁻²⁴ the investigators at 17 sites across 14 U.S. states (**Table E1**) enrolled infants hospitalized with an attending physician diagnosis of bronchiolitis during one of three consecutive bronchiolitis seasons from November 1 to April 30 (2011-2014). Bronchiolitis was defined by the American Academy of Pediatrics (AAP) guidelines—acute respiratory illness with some combination of rhinitis, cough, tachypnea, wheezing, crackles, and retractions.²⁶ We excluded infants with known heart-lung disease, immunodeficiency, immunosuppression, or gestational age <32 weeks. All patients were treated at the discretion of the treating physician. Of 1,016 infants initially enrolled into the MARC-35 cohort, 921 (91%) completed the run-in procedures (i.e., contact at both 1-week after hospital discharge and 3-weeks after hospitalization) and, therefore, comprised the longitudinal cohort. The institutional review board at each participating hospital approved the study. Written informed consent was obtained from the parent or guardian.

Data Collection

Investigators conducted a structured interview that assessed patients' demographic characteristics, medical, environmental, and family history, and details of the bronchiolitis course. After the index hospitalization for bronchiolitis, we conducted parental interviews by

telephone at 6-month intervals, reviewed medical records (trained physicians only), and performed in-person exam at age 3 years to ascertain anthropomorphic measures (with the use of standard clinical scale and clinical protocol by trained staff). All data were reviewed at the EMNet Coordinating Center at Massachusetts General Hospital (Boston, MA), and site investigators were queried about missing data and discrepancies identified by manual data checks.

Exposures

The primary exposure was growth trajectory of individual children—defined by the changes in BMI-for-age in the first 3 years of life (measured at birth [age 0 month], ages 6, 12, 15, 18, 24, and 36 months). At each of the 7 timepoints, we computed BMI-for-age and BMI z-score-for-age (BMIZ-for-age) based on the age- and sex-specific reference values of the World Health Organization (WHO) (age ≤ 2 years) and the Center for Disease Control and Prevention (CDC) (age > 2 years) child growth standards,^{27,28} according to the AAP recommendation.²⁹

Outcome Measure

The primary outcome was development of asthma by age 5 years. Asthma was defined using a commonly-used epidemiologic definition³⁰: physician-diagnosis of asthma, with either asthma medication use (e.g., inhaled bronchodilators, inhaled corticosteroids, leukotriene receptor antagonists; **Table E2**) or asthma-related symptoms (e.g., wheezing, nocturnal cough) in the preceding year.

Statistical Analyses

First, to identify mutually-exclusive profiles of growth trajectory during the first 3 years of life, we applied a unsupervised clustering (longitudinal k-means clustering) approach³¹ based on the Euclidian distance to individual longitudinal trajectories of BMI-for-age. The number of profiles was chosen based on Calinski-Harabasz methods (**Figure E1**) and clinical plausibility.³²⁻
³⁴ We categorized patients into five groups, excluding 41 infants with <2 anthropomorphic measurements (4%). Missing measurements are imputed by the use of linear interpolation with variation to make the trajectory follow the shape of the sample's mean trajectory.³¹

We examined the between-profile differences in the patient characteristics and clinical presentation by using Kruskal-Wallis, χ^2 , and Fisher exact tests as appropriate. Next, to examine the association of derived growth trajectory profiles with the risk of developing asthma, we constructed unadjusted and adjusted mixed-effect logistic regression models that account for between-hospital differences. In the multivariable model, we adjusted for patient-level potential confounders (sex, race/ethnicity, prematurity, history of eczema, cigarette smoke exposure, parental history of asthma, parental history of eczema, and allergic sensitization [defined by ≥ 1 positive value for allergen-specific IgE]). We chose these covariates on the basis of *a priori* knowledge.^{35,36} Additionally, based on an *a priori* definition,³⁷ we also stratified the analysis by allergic predisposition (i.e., parental history of asthma or eczema, or child allergic sensitization).

Sensitivity Analyses

To determine the robustness of our inference, we conducted a series of sensitivity analyses. Firstly, we computed E-values to determine the robustness of inference to potential unmeasured confounding by using R *EValue* package.³⁸ The E-value represents the minimum magnitude of association that an unmeasured confounder would need to have in order to fully

189 explain the association of interest, conditional on the covariates. For example, an E-value of 2.0
190 means that the odds ratio (OR) for the association of an unmeasured confounder with both the
191 exposure and outcome would have to be ≥ 2.0 to explain away the observed exposure-outcome
192 association. Secondly, we examined the linear association of growth trajectory profiles (as
193 ordinal variable) with asthma risk. Thirdly, we used an inverse probability treatment weighting
194 method (IPTW) to estimate the causal relation of trajectory profiles with the outcome. The IPTW
195 for the five trajectory profiles were estimated from the generalized boosted model by using R
196 *twang* package.³⁹ Fourthly, to account for potential selection bias due to censoring, we used an
197 inverse probability censoring weighting method (IPCW).^{40,41} Fifthly, we repeated the analysis in
198 the two major virus groups—respiratory syncytial virus (RSV) and rhinovirus. Lastly, we also
199 examined the robustness of associations using different numbers of profiles. We used an alluvial
200 plot to visualize consistencies across the different numbers (4, 5, or 6 growth trajectory profiles),
201 and repeated the regression analysis. Analysis used R version 4.0.2. All P-values were two-
202 tailed, with $P < 0.05$ considered statistically significant.

RESULTS

Patient characteristics

Of 921 infants in the longitudinal cohort, 880 (96%) had sufficient data to derive growth trajectories and were eligible for the current analysis. The analytic and non-analytic cohorts did not differ in baseline characteristics, except that the proportion of daycare use was higher in the analytic cohort (**Table E3**). Among the analytic cohort, 40% were female; 44% were non-Hispanic white, 23% non-Hispanic black, and 29% Hispanic (**Table 1**). Additionally, the median birth weight was 3.3 kg (IQR 2.9-3.6 kg) and 82% had RSV infection. Overall, 27% developed asthma by age 5 years.

Longitudinal clustering identified five distinct growth profiles

An application of the longitudinal clustering method to the BMI-for-age in the first three years of life identified five distinct profiles: persistent low growth (profile A, 27%), normative growth (profile B, 33%), transient overweight (profile C, 21%), late-onset overweight (profile D, 16%), and persistent obesity (profile E, 3%) profiles (**Figure 1**). The children classified as profile B had a more or less flat line within a range of approximately ± 0.5 BMIz-for-age (i.e., approximately normative growth defined in the age- and sex-specific WHO and CDC definitions).⁴² Therefore, this profile is referred to the normative trajectory profile, and used as the reference for the following analysis.

Table 1 summarizes the patient characteristics and clinical course of bronchiolitis by growth trajectory. For example, children with a persistent low growth profile were more likely to be female with a lower birth weight ($P < 0.05$). In contrast, the children with a persistent obesity profile had a higher prevalence of eczema and allergic sensitization ($P < 0.05$). There were no

significant differences in the causative virus of the index episode of bronchiolitis nor in the clinical course.

Growth trajectory profiles and risks of developing asthma

In the multivariable model adjusting for eight confounders and site effects, compared to the normative growth (profile B) children, the persistent obesity (profile E) children had a significantly higher risk of developing asthma (24% vs. 38%, OR 2.55, 95%CI 1.07-6.09, $P=0.03$, E-value 2.58; **Figure 2**). While the children with a transient overweight (profile C, 27%) and late-onset overweight (profile D, 31%) profiles appeared to have a dose-dependent relationship with the outcome risk, the associations were not statistically significant.

Among the children with a persistent obesity profile, in a stratified analysis with limited statistical power, those without allergic predisposition had a significantly higher risk of asthma. This was true both among children with versus without a parental allergic history (15% vs. 35%, OR 3.02, 95%CI 1.05-8.64, $P=0.04$, E-value 2.86; **Table 2**) and those with versus without IgE sensitization (22% vs. 35%, OR 3.18, 95%CI 1.02-9.92, $P=0.047$, E-value 2.96 in the non-IgE sensitization group, **Table 3**). By contrast, among infants with allergic predisposition, the risk of asthma did not differ between the profiles ($P>0.05$).

Sensitivity analyses

The sensitivity analyses supported the robustness of the findings. In the analysis modeling the growth trajectory profiles as an ordinal variable, there was a linear association between accelerated growth and asthma risk (OR 1.16 per a transition to an upper profile [e.g., from profile B to C], 95% CI 1.01-1.34, $P=0.04$, E-value 1.37; **Table E4**). The persistent obesity

results were also consistent with the use of IPTW (OR 2.65, 95% CI 1.08-6.52, $P=0.03$, E-value 2.64) and IPCW (OR 2.65, 95% CI 1.08-6.51, $P=0.03$, E-value 2.64; **Table E5**). In the subgroup analysis of the two major virus groups, the findings did not materially change. For example, the persistent obesity profile had a significantly higher risk of developing asthma in the RSV group (OR 3.97, 95%CI 1.55-10.2, $P=0.004$, E-value 3.39) and a non-significantly higher risk in the rhinovirus group with limited power (OR 4.60, 95%CI 0.40-52.8, $P=0.22$; **Table E6**).

Lastly, the alluvial plot (**Figure E2**) demonstrated a consistency of the original trajectory profiles across the different numbers chosen (4, 5, or 6 trajectory profiles). Similar to the primary analysis, with the use of 6 growth trajectory profiles, the risk of asthma development was higher in the profile 6 (which is concordant to the profile E [persistent overweight profile]) with an OR of 2.62 (95% CI 1.03-6.68, $P=0.04$, E-value 2.62; **Table E7**).

DISCUSSION

In this prospective multicenter cohort of 880 infants hospitalized with bronchiolitis, our longitudinal clustering identified five distinct growth trajectory profiles in their first three years of life. Compared to children with a normative growth profile, those with a persistent obesity profile had a significantly higher risk of developing asthma. With the stratification by allergic predisposition, only the persistent obesity profile children who did not have parental history of asthma or eczema, nor IgE sensitization during infancy, had a significantly higher risk of asthma. The observed associations persisted across different analytical assumptions. To the best of our knowledge, this is the first investigation that determined the longitudinal associations between growth trajectories in the early childhood and the risk of developing asthma among infants hospitalized with bronchiolitis—a large population with substantial morbidity burden.

Overweight and obesity have been recognized as a major risk marker and potential causal factor for asthma for more than 20 years.¹¹ This relation is complex, however, and “obese-asthma syndrome” consists of multiple subgroups (e.g., *de novo* asthma, asthma modified by obesity, and obesity predisposed by asthma).⁸ Yet, studies have suggested the causal link from (anthropomorphically-defined) overweight/obesity to asthma inception.^{9,10} Indeed, in agreement with our findings, studies have shown that birth weight of ≥ 4500 grams¹³ and BMI-for-age of $\geq 85^{\text{th}}$ percentile during toddlerhood^{12,14,15,43} are associated with a higher risk of developing asthma. By contrast, other studies have also reported that a lower birth weight is associated with an elevated risk of asthma^{16,17} and that early life weight gain is not associated with increased risk.^{18,19} Although these studies had added invaluable information, their inferences were limited due to the single anthropomorphic measurement. As the body proportion rapidly changes in the early childhood, it is important to take the longitudinal growth trajectory into consideration.

Recently, several studies have suggested associations of growth trajectories with asthma development in non-high risk populations.^{33,44,45} Additionally, the Melbourne Atopy Cohort Study also reported that, in 620 infants with a family history of allergic diseases, those with an “early-low and catch-up” or “persistently-high” BMI trajectory in the first 2 years of life had an increased risk of asthma, lower FEV₁/FEV ratio, and higher fractional exhaled nitric oxide levels at age 18 years.³² The apparent discrepancy in the inference may be attributable to the difference in the target population, study design, setting, measurements, outcome definition, or any combination of these factors. Furthermore, these earlier studies did not examine the interrelations between growth trajectory, allergic predisposition, and incident asthma in children. Using the data of a large racially/ethnically diverse U.S. cohort of infants hospitalized for bronchiolitis, the current study corroborates these earlier findings. It also extends them by investigating the longitudinal relationship of the growth trajectory with the asthma risk and its effect modification by allergic predisposition.

The mechanisms underlying the observed associations between growth trajectory profile and development of asthma warrant clarification. First, emerging evidence suggests the role of adiposopathy—“sick fat” or adipose tissue dysfunction—in the pathogenesis of complex disease conditions including asthma.^{46,47} Adiposopathy is characterized by impaired adipogenesis, altered lipid metabolism, and adipose/systemic inflammation (e.g., upregulated IL-6 pathway and T_H1 polarization),^{8,47} which is different from allergic inflammation (e.g., T_H2 polarization and type 2 inflammation). Second, a recent genome-wide association study has demonstrated positive genetic correlations of obesity traits with non-allergic asthma, but not with allergic asthma,⁶ indicating a shared genetic component between obesity and non-allergic asthma. Third, a small case-control study has also reported that obese children with asthma had distinctive blood

epigenetic signatures (e.g., DNA methylation modifications in genes related to T_H1 polarization).⁴⁸ Other potential mechanisms include obesity-related metabolic abnormalities, alterations in the gut microbiome, and changes in the airway structures and function.⁸ Moreover, these mechanisms are not mutually exclusive. Notwithstanding the complexity, the identification of relationships between growth trajectory and non-allergic predisposition in the early childhood with the development of asthma is an important finding.

Our study has several potential limitations. First, 4% of the longitudinal cohort were excluded from the analysis due to the lack of anthropomorphic or outcome measures. Yet, the analytical and non-analytical cohorts did not materially differ. Additionally, the results were consistent with the use of IPCW, thereby collectively arguing against substantial selection bias. Second, the current study did not have “healthy controls”. However, we note that the study objective was to examine the longitudinal relationship of growth trajectories with asthma *among* infants hospitalized with bronchiolitis, of which 30% will subsequently develop asthma.²⁻⁵ Third, while the study utilized anthropomorphic measures at multiple time points, we were unable to examine the immunological status that is related to obesity or adiposopathy (e.g., adiposopathy-related cytokines including IL-1 β , IL-6, and leptin).^{8,49} Fourth, the current study does not have information on subsequent bronchiolitis hospitalizations, while it is possible for infants to be hospitalized multiple times in one season. Fifth, as with any observational study, causal inferences could be confounded by unmeasured factors, such as diet, sleep status, and amount of corticosteroid exposure. Regardless, the large E-values support the robustness of evidence. Lastly, even with the racially/ethnically and geographically diverse U.S. sample, the inferences must be cautiously generalized beyond children hospitalized with bronchiolitis. Nevertheless, the data remain directly relevant to 110,000 hospitalized U.S. children each year.¹

Conclusions

In this prospective multicenter cohort of 880 infants hospitalized with bronchiolitis, we identified distinct growth trajectory profiles in the first three years of life that have differential risks for developing asthma. In particular, children with a persistent obesity profile had the highest probability. This association was only observed in children without allergic predisposition in infancy. For researchers, our data should facilitate further investigations into the mechanisms underlying the obesity-non-allergic asthma link during the early childhood, a critical period of airway development. For clinicians, our data not only provide an evidence base for early identification of children at highest risk for asthma development, but also may offer opportunities for early targeted interventions for asthma prevention (e.g., those on nutrition, physical activity, and sleep^{50,51}) in this high-risk population.

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Table 1. Baseline characteristics and clinical course of infants hospitalized with bronchiolitis, according to growth trajectory profiles

Characteristics	Overall (n=880; 100%)	A) Persistent low growth profile (n=236; 27%)	B) Normative growth profile (n=293; 33%)	C) Transient overweight profile (n=181; 21%)	D) Late-onset overweight profile (n=141; 16%)	E) Persistent obesity profile (n=29; 3%)	P-value
Demographics							
Age (month), median (IQR)	3 (2-6)	3 (2-6)	3 (1-6)	3 (2-6)	3 (2-6)	4 (2-7)	0.27
Female sex	351 (40)	123 (52)	117 (40)	54 (30)	46 (33)	11 (38)	<0.001
Race/ethnicity							0.22
Non-Hispanic white	387 (44)	116 (49)	129 (44)	74 (41)	57 (40)	11 (38)	
Non-Hispanic black	202 (23)	53 (23)	70 (24)	40 (22)	32 (23)	7 (24)	
Hispanic	257 (29)	52 (22)	85 (29)	61 (34)	49 (35)	10 (35)	
Other or unknown	34 (4)	15 (6)	9 (3)	6 (3)	3 (2)	1 (3)	
C-section delivery	300 (34)	81 (34)	105 (36)	66 (36)	40 (28)	8 (28)	0.55
Prematurity (32–36.9 weeks)	162 (18)	51 (22)	45 (15)	31 (17)	31 (22)	4 (14)	0.26
Birth weight (kg), median (IQR)	3.3 (2.9-3.6)	3.1 (2.7-3.4)	3.4 (3.0-3.6)	3.4 (3.1-3.7)	3.1 (2.7-3.4)	3.4 (3.1-3.8)	<0.001
History of eczema	127 (14)	39 (17)	34 (11)	18 (10)	29 (21)	7 (24)	0.02
Ever attended daycare	208 (24)	55 (23)	72 (25)	37 (20)	38 (27)	6 (21)	0.70
Cigarette smoke exposure at home	130 (15)	38 (16)	44 (15)	24 (13)	21 (15)	3 (10)	0.89
Maternal smoking during pregnancy	122 (14)	36 (15)	37 (13)	20 (11)	26 (18)	3 (10)	0.33
Parental history of asthma	285 (32)	81 (34)	98 (33)	50 (28)	49 (35)	7 (24)	0.45
Parental history of eczema	163 (19)	53 (23)	52 (18)	33 (18)	20 (14)	5 (17)	0.36
Clinical presentation at index hospitalization							
Respiratory virus							
RSV	722 (82)	193 (82)	250 (85)	136 (75)	118 (84)	25 (86)	0.07

Rhinovirus	177 (20)	38 (16)	57 (20)	49 (27)	29 (21)	4 (14)	0.07
Other pathogen*	203 (23)	49 (21)	65 (22)	45 (25)	37 (26)	7 (24)	0.74
Laboratory data							
Blood eosinophilia ($\geq 4\%$)	80 (9)	25 (11)	24 (8)	19 (10)	11 (8)	1 (3)	0.66
Allergic (specific immunoglobulin E) sensitization†	172 (20)	47 (20)	60 (21)	34 (19)	19 (14)	12 (41)	0.02
Clinical course							
Positive pressure ventilation use‡	48 (6)	13 (6)	22 (8)	5 (3)	6 (4)	2 (7)	0.25
Intensive treatment use§	135 (15)	30 (13)	58 (20)	22 (12)	20 (14)	5 (17)	0.12

Abbreviations: IQR, interquartile range; RSV, respiratory syncytial virus

Data are no. (%) of infants, unless otherwise indicated. Percentages may not equal 100 because of rounding and missingness.

* Adenovirus, bocavirus, *Bordetella pertussis*, enterovirus, human coronavirus NL63, OC43, 229E, or HKU1, human metapneumovirus, influenza A or B virus, *Mycoplasma pneumoniae*, and/or parainfluenza virus 1-3.

† Defined by having one or more positive values for allergen-specific IgE

‡ Defined as the use of invasive and/or non-invasive mechanical ventilation (e.g., continuous positive airway pressure ventilation).

§ Defined as the use of positive pressure ventilation and/or intensive care unit admission.

Table 2. Unadjusted and adjusted associations of growth trajectory profiles with development of asthma, according to parental history of asthma and eczema status

Growth trajectory profiles and strata	Number of outcomes, n (%)	Unadjusted model*		Adjusted model*, †		
		Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	E-value (CI limit) ‡
No parental history of asthma or eczema [§] (n=518)						
A: Persistent low growth profile(n=130)	18 (14%)	0.90 (0.46-1.72)	0.75	0.91 (0.47-1.77)	0.78	-
B: Normative growth profile (n=168)	25 (15%)	[Reference]		[Reference]		-
C: Transient overweight profile (n=114)	22 (19%)	1.36 (0.72-2.56)	0.34	1.31 (0.69-2.49)	0.41	-
D: Late-onset overweight profile (n=86)	20 (23%)	1.84 (0.94-3.57)	0.07	1.71 (0.87-3.38)	0.12	-
E: Persistent obesity profile (n=20)	7 (35%)	3.17(1.09-8.71)	0.03	3.02 (1.05-8.64)	0.04	2.86 (1.19)
Parental history of asthma or eczema [§] (n=362)						
A: Persistent low growth profile (n=106)	38 (36%)	1.11 (0.64-1.93)	0.70	1.15 (0.65-2.06)	0.63	-
B: Normative growth profile (n=125)	44 (35%)	[Reference]		[Reference]		-
C: Transient overweight profile (n=67)	27 (40%)	1.33 (0.71-2.46)	0.37	1.26 (0.66-2.41)	0.48	-
D: Late-onset overweight profile (n=55)	20 (36%)	1.21 (0.61-2.37)	0.58	1.03 (0.50-2.11)	0.94	-
E: Persistent obesity profile (n=9)	4 (44%)	1.82 (0.41-8.03)	0.41	1.58 (0.39-6.95)	0.55	-

Abbreviation: CI, confidence interval

* Regression models with a complete case analysis excluding patients with missing outcome: 3 in profile A, 7 in profile B, 4 in profile C, 7 in profile D, and 1 in profile E among the non-parental history of asthma or eczema strata; 6 in profile A, 1 in profile B, 3 in profile C, 5 in profile D, and 1 in profile E in the parental history of asthma or eczema strata.

† Adjusted for sex, race/ethnicity, prematurity (32–36.9 weeks), history of eczema, cigarette smoke exposure at home, and allergic sensitization.

‡ The E-value (with its lower 95% CI bound) represents how strongly an unmeasured confounder would have to be associated with the exposure and outcome in order for the observed association to be independent.

§ Defined as having or not having parental history of asthma and/or eczema.

Table 3. Unadjusted and adjusted associations of growth trajectory profiles with development of asthma, according to IgE sensitization status at index hospitalization

Growth trajectory profiles and strata	Number of outcomes, n (%)	Unadjusted model*		Adjusted model*, †		
		Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	E-value (CI limit)*
No IgE sensitization§ (n=708)						
A: Persistent low growth profile (n=189)	45 (24%)	1.13 (0.72-1.79)	0.59	1.17 (0.72-1.91)	0.52	-
B: Normative growth profile (n=233)	51 (22%)	[Reference]		[Reference]		-
C: Transient overweight profile (n=147)	39 (27%)	1.32 (0.81-2.10)	0.26	1.35 (0.81-2.25)	0.25	-
D: Late-onset overweight profile (n=122)	38 (31%)	1.75 (1.06-2.88)	0.03	1.62 (0.95-2.77)	0.08	-
E: Persistent obesity profile (n=17)	6 (35%)	2.30 (0.74-6.69)	0.13	3.18 (1.02-9.92)	0.047	2.96 (1.10)
IgE sensitization§ (n=164)						
A: Persistent low growth profile (n=45)	11 (24%)	0.72 (0.29-1.71)	0.46	0.66 (0.24-1.79)	0.42	-
B: Normative growth profile (n=58)	18 (31%)	[Reference]		[Reference]		-
C: Transient overweight profile (n=33)	10 (30%)	0.97 (0.37-2.42)	0.94	1.12 (0.41-3.06)	0.83	-
D: Late-onset overweight profile (n=16)	2 (13%)	0.32 (0.05-1.30)	0.16	0.42 (0.08-2.22)	0.32	-
E: Persistent obesity profile (n=12)	5 (42%)	1.59 (0.42-5.67)	0.48	1.38 (0.33-5.77)	0.66	-

Abbreviations: CI, confidence interval; IgE, immunoglobulin E

* Regression models with a complete case analysis excluding patients with missing outcome: 7 in profile A, 6 in profile B, 6 in profile C, 9 in profile D, and 2 in profile E in the non-IgE sensitization strata; 2 in profile A, 2 in profile B, 1 in profile C, 3 in profile D, and 0 in profile E in the IgE sensitization strata.

[†] Adjusted for sex, race/ethnicity, prematurity (32–36.9 weeks), history of eczema, and cigarette smoke exposure at home.

[‡] The E-value (with its lower 95% CI bound) represents how strongly an unmeasured confounder would have to be associated with the exposure and outcome in order for the observed association to be independent.

[§] Defined as having or not having IgE sensitization at the index hospitalization.

FIGURE LEGENDS

Figure 1. Growth trajectory profiles during ages 0 to 36 months

To identify mutually exclusive profiles of growth trajectory during the first three years of life, we applied a longitudinal k-means clustering approach to the individual longitudinal trajectories of BMI. The number of profiles was chosen based on the Calinski-Harabasz index (**Figure E1**) and clinical plausibility. We categorized patients into five groups: A) persistent low growth profile (n=236); B) normative growth profile (the reference group) (n=293); C) transient overweight profile (n=181); D) late-onset overweight profile (n=141); and E) persistent obesity profile (n=29).

The x-axis indicates age (months); the y-axis indicates BMI z-score (according to the WHO [age ≤ 2 years] and CDC [age > 2 years] child growth standards). The dotted horizontal lines indicate the following threshold percentiles of BMI z-score (5th percentile [underweight], 50th percentile, 85th percentile [overweight], and 95th percentile [obesity]). The fitted lines represent locally estimated scatterplot smoothed (loess) curves of BMI z-score of each profile. The circles represent the mean BMI z-score of the corresponding profile at one of the ages (0, 6, 12, 15, 18, 24, and 36 months).

Abbreviation: BMI, body mass index

Figure 2. Unadjusted and adjusted associations of growth trajectory profiles with development of asthma

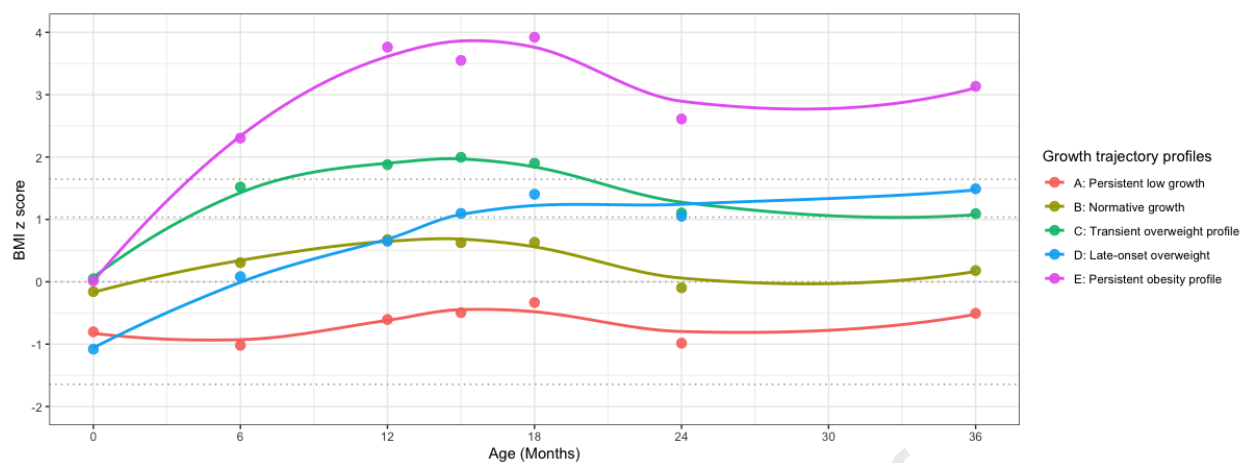
The risk of developing asthma in the profile B (normative growth profile—the reference group) was compared with each of the other growth trajectory profiles: A (persistent low growth profile), C (transient overweight profile), D (late-onset overweight profile), and E (persistent obesity profile).

* Regression models with a complete case analysis excluding patients with missing outcome: 9 in profile A, 8 in profile B, 7 in profile C, 12 in profile D, and 2 in profile E. This missingness is addressed by the use of inverse probability censoring weighting method (see **Table E5**).

† The E-value (with its lower 95% CI bound) represents how strongly unmeasured confounder(s) would have to be associated with the exposure and outcome in order for the observed association to be independent.

‡ Mixed-effects models adjusting for eight potential confounders (sex, race/ethnicity, prematurity, history of eczema, cigarette smoke exposure at home, parental history of asthma, parental history of eczema, and allergic sensitization) and accounting for potential patient clustering within the hospitals.

Abbreviations: BMI, body mass index; CI, confidence interval



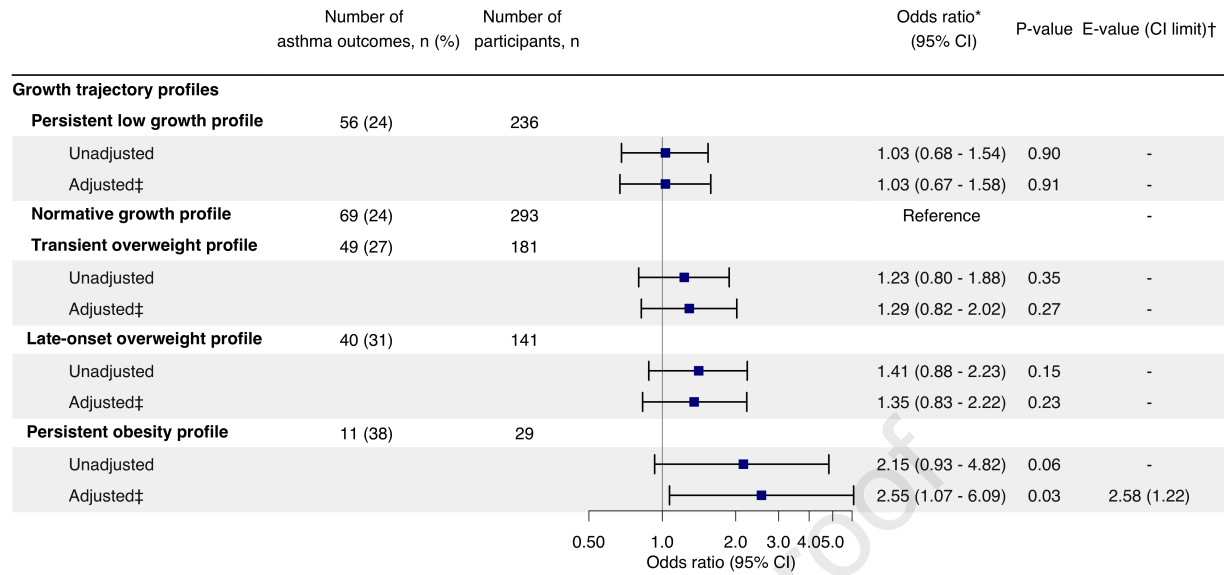


Figure E1. Calinski-Harabasz index according to number of growth trajectory profiles

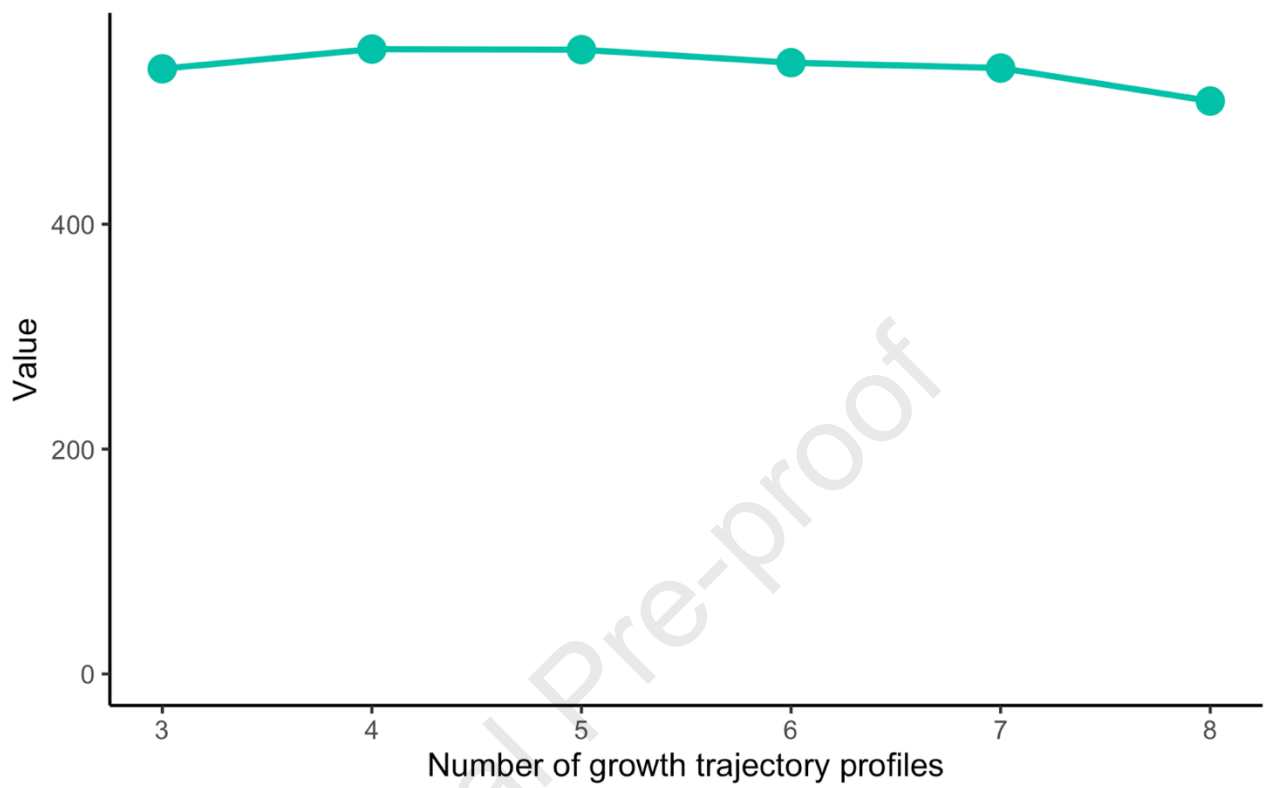
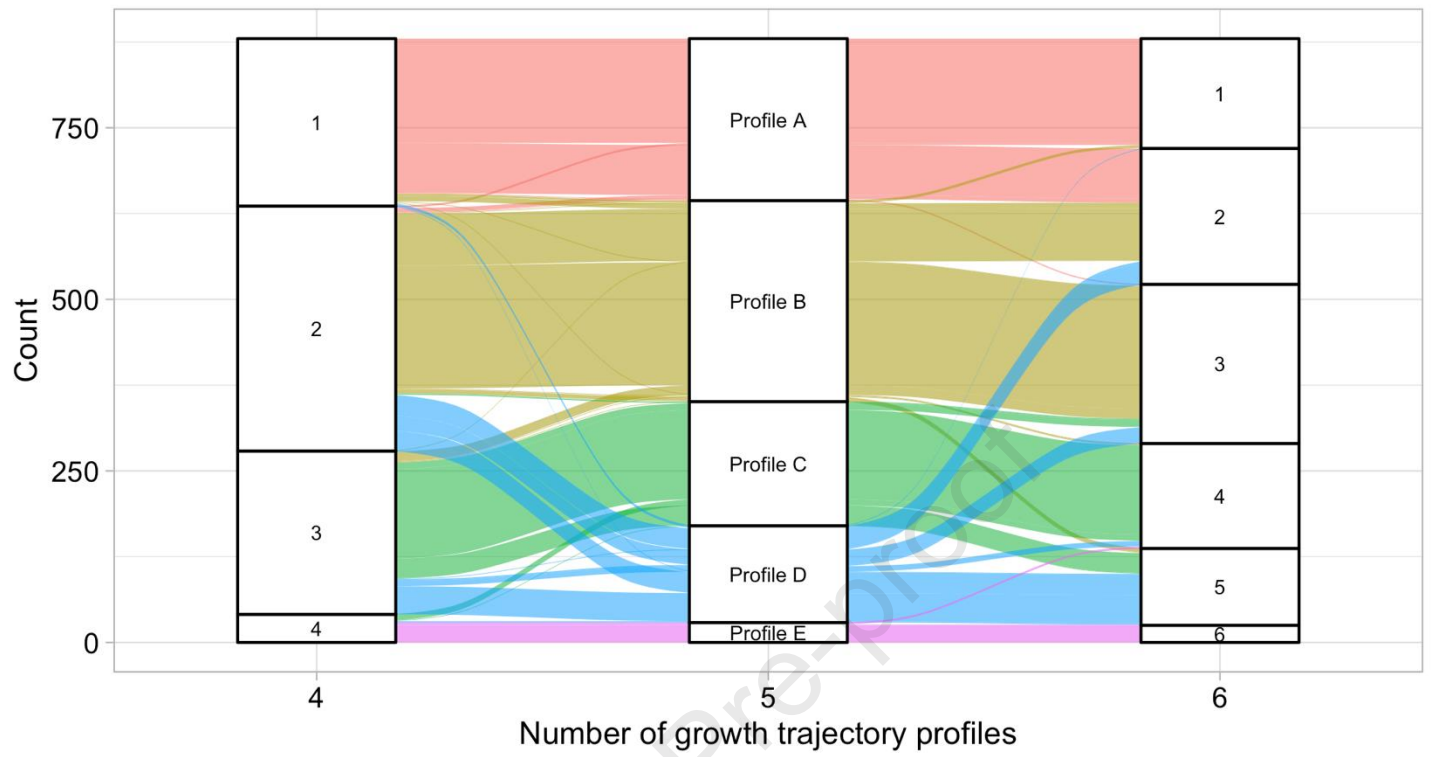


Figure E2. Alluvial plot to examine consistencies across different numbers of growth trajectory profiles

SUPPLEMENTARY ONLINE CONTENT**Association of growth trajectory profiles with asthma development in infants hospitalized with bronchiolitis: A multicenter prospective study**

Makiko Nanishi MD; Michimasa Fujiogi MD; Michelle Stevenson MD; Liming Liang, PhD; Ying Qi, MPH; Yoshihiko Raita MD, MPH, MMSc; Kohei Hasegawa MD, MPH; and Carlos A. Camargo Jr. MD, DrPH

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Figure E1. Calinski-Harabasz index according to number of growth trajectory profiles

Figure E2. Alluvial plot to examine consistencies across different numbers of growth trajectory profiles

Table E1. Principal investigators at the 17 participating sites in MARC-35

Amy D. Thompson, MD	Alfred I. duPont Hospital for Children, Wilmington, DE
Federico R. Laham, MD, MS	Arnold Palmer Hospital for Children, Orlando, FL
Jonathan M. Mansbach, MD, MPH	Boston Children's Hospital, Boston, MA
Vincent J. Wang, MD, MHA and Susan Wu, MD	Children's Hospital of Los Angeles, Los Angeles, CA
Michelle B. Dunn, MD and Jonathan M. Spergel, MD, PhD	Children's Hospital of Philadelphia, Philadelphia, PA
Juan C. Celedón, MD, DrPH	Children's Hospital of Pittsburgh, Pittsburgh, PA
Michael R. Gomez, MD, MS-HCA and Nancy Inhofe, MD	The Children's Hospital at St. Francis, Tulsa, OK
Brian M. Pate, MD and Henry T. Puls, MD	The Children's Mercy Hospital & Clinics, Kansas City, MO
Stephen J. Teach, MD, MPH	Children's National Medical Center, Washington, D.C.
Richard T. Strait, MD and Stephen C. Porter, MD, MSc, MPH	Cincinnati Children's Hospital and Medical Center, Cincinnati, OH
Ilana Y. Waynik, MD	Connecticut Children's Medical Center, Hartford, CT
Sujit Iyer, MD	Dell Children's Medical Center of Central Texas, Austin, TX
Michelle D. Stevenson, MD, MS	Norton Children's Hospital, Louisville, KY
Margaret Samuels-Kalow, MD, MPhil, Wayne G. Shreffler, MD, PhD, Ari R. Cohen, MD	Massachusetts General Hospital, Boston, MA
Anne K. Beasley, MD and Cindy S. Bauer, MD	Phoenix Children's Hospital, Phoenix, AZ
Thida Ong, MD and Markus Boos, MD, PhD	Seattle Children's Hospital, Seattle, WA
Charles G. Macias, MD, MPH	Texas Children's Hospital, Houston, TX

Table E2. Asthma definition by medication in the overall cohort and each of the growth trajectory profiles

	Overall	A)	B)	C)	D)	E)	
		Persistent low growth profile	Normative growth profile	Transient overweight profile	Late-onset overweight profile	Persistent obesity profile	P- value
Medication	(n=880)	(n=236)	(n=293)	(n=181)	(n=141)	(n=29)	
Inhaled bronchodilator	179 (20)	48 (20)	54 (18)	38 (21)	29 (21)	10 (35)	0.41
Inhaled corticosteroids	105 (12)	34 (14)	29 (10)	22 (12)	15 (11)	5 (17)	0.24
Leukotriene receptor antagonists	52 (6)	13 (6)	17 (6)	10 (6)	11 (8)	1 (3)	0.56

Table E3. Comparisons between analytic and non-analytic cohorts in MARC-35

Characteristics	Analytic cohort (n=880)	Non-analytic cohort (n=41)	P-value
Demographics			
Age (month), median (IQR)	3 (2-6)	3 (2-7)	0.47
Female sex	351 (40)	16 (39)	1.00
Race/ethnicity			
Non-Hispanic white	387 (44)	14 (34)	
Non-Hispanic black	202 (23)	8 (20)	
Hispanic	257 (29)	18 (44)	
Other or unknown	34 (4)	1 (2)	
C-section delivery	300 (34)	12 (29)	0.68
Prematurity (32-36.9 weeks)	162 (18)	9 (22)	0.72
History of eczema	127 (14)	10 (24)	0.13
Ever attended daycare	208 (24)	3 (7)	0.03
Cigarette smoke exposure at home	130 (15)	8 (20)	0.54
Maternal smoking during pregnancy	122 (14)	4 (10)	0.63
Parental history of asthma	285 (32)	20 (49)	0.05
Parental history of eczema	163 (19)	12 (29)	0.13
Clinical presentation			
Respiratory virus			
RSV	722 (82)	30 (73)	0.22
Rhinovirus	177 (20)	9 (22)	0.93
Other pathogen*	203 (23)	6 (15)	0.29
Laboratory data			
Blood eosinophilia ($\geq 4\%$)	80 (9)	2 (5)	0.50
Allergic (specific immunoglobulin E) sensitization [†]	172 (20)	10 (24)	0.58
Clinical course			
Positive pressure ventilation use [‡]	48 (6)	1 (2)	0.63
Intensive treatment use [§]	135 (15)	6 (15)	1.00

Abbreviations: IQR, interquartile range; RSV, respiratory syncytial virus

Data are no. (%) of infants, unless otherwise indicated. Percentages may not equal 100 because of rounding and missingness.

* Adenovirus, bocavirus, *Bordetella pertussis*, enterovirus, human coronavirus NL63, OC43, 229E, or HKU1, human metapneumovirus, influenza A or B virus, *Mycoplasma pneumoniae*, and/or parainfluenza virus 1-3.

[†] Defined by having one or more positive values for allergen-specific IgE.

[‡] Defined as use of invasive and/or non-invasive mechanical ventilation (e.g., continuous positive airway pressure ventilation).

[§] Defined as use of positive pressure ventilation and/or intensive care unit admission.

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Table E4. Unadjusted and adjusted associations of growth trajectory profiles (as ordinal variable) with development of asthma

	Unadjusted model		Adjusted model*		
	Odds ratio (95% CI) [†]	P-value	Odds ratio (95% CI) [†]	P-value	E-value (CI limit) [‡]
Growth trajectory profiles	1.15 (1.01-1.32)	0.04	1.16 (1.01-1.34)	0.04	1.37 (1.06)

Abbreviation: CI, confidence interval

* Adjusted for sex, race/ethnicity, prematurity (32–36.9 weeks), history of eczema, cigarette smoke exposure at home, parental history of asthma, and parental history of eczema, and allergic sensitization.

[†] Odds ratios are estimated per each incremental increase in the growth trajectory profiles (i.e., comparing the profile A [the reference] with the profiles B, C, D, and E as an ordinal variable in an ascending order).

[‡] The E-value (with its lower 95% confidence interval bound) represents how strongly an unmeasured confounder would have to be associated with the exposure and outcome in order for the observed association to be independent.

Table E5. Unadjusted and adjusted associations of growth trajectory profiles with development of asthma by using inverse probability treatment and censoring weighting methods

Growth trajectory profile	Unadjusted model		Adjusted model*		
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	E-value (CI limit) [†]
Inverse probability treatment weighting method[‡]					
A: Persistent low growth profile	0.95 (0.62-1.46)	0.82	1.02 (0.64-1.63)	0.92	-
B: Normative growth profile	[Reference]		[Reference]		-
C: Transient overweight profile	1.13 (0.73-1.75)	0.58	1.24 (0.78-1.97)	0.36	-
D: Late-onset overweight profile	1.15 (0.71-1.88)	0.57	1.26 (0.75-2.10)	0.38	-
E: Persistent obesity profile	1.99 (0.86-4.64)	0.11	2.65 (1.08-6.52)	0.03	2.64 (1.24)
Inverse probability censoring weighted method[§]					
A: Persistent low growth profile	0.95 (0.62-1.45)	0.81	1.02 (0.64-1.61)	0.95	-
B: Normative growth profile	[Reference]		[Reference]		-
C: Transient overweight profile	1.13 (0.73-1.75)	0.57	1.25 (0.79-1.98)	0.35	-
D: Late-onset overweight profile	1.17 (0.72-1.92)	0.52	1.27 (0.76-2.12)	0.36	-
E: Persistent obesity profile	2.00 (0.86-4.64)	0.11	2.65 (1.08-6.51)	0.03	2.64 (1.25)

Abbreviation: CI, confidence interval

* Adjusted for sex, race/ethnicity, prematurity (32–36.9 weeks), history of eczema, cigarette smoke exposure at home, parental history of asthma, and parental history of eczema, and allergic sensitization.

[†] The E-value (with its lower 95% confidence interval bound) represents how strongly an unmeasured confounder would have to be associated with the exposure and outcome in order for the observed association to be independent.[‡] Inverse probabilities of treatment were estimated by using a generalized boosted regression modeling that includes sex, race/ethnicity, annual household income, health insurance type (public, private, and others), C-section delivery, prematurity (32–36.9 weeks), history of eczema, ever attended daycare, cigarette smoke exposure at home, maternal smoking during pregnancy, breast-feeding, parental history of asthma, parental history of eczema, and allergic sensitization.[§] Inverse probabilities of censoring were estimated by using a logistic regression model that includes age, sex, race/ethnicity, parent history of asthma, previous breathing problems before the index hospitalization, and year of enrollment.

Table E6. Unadjusted and adjusted associations of growth trajectory profiles with development of asthma, according to infecting virus

Growth trajectory profiles and virus	Number of outcomes, n (%)	Unadjusted model*		Adjusted model*,†		
		Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	E-value (CI limit) ‡
RSV infection (n=691*)						
A: Persistent low growth profile (n=186)	45 (24%)	1.28 (0.81-2.02)	0.29	1.29 (0.79-2.08)	0.31	-
B: Normative growth profile (n=245)	49 (20%)	[Reference]		[Reference]		-
C: Transient overweight profile (n=131)	31 (24%)	1.24 (0.74-2.06)	0.41	1.30 (0.76-2.22)	0.34	-
D: Late-onset overweight profile (n=106)	29 (27%)	1.51 (0.88-2.55)	0.13	1.46 (0.83-2.55)	0.18	-
E: Persistent obesity profile (n=23)	10 (44%)	3.08(1.25-7.42)	0.01	3.97 (1.55-10.2)	0.004	3.39 (1.79)
Rhinovirus infection (n=168*)						
A: Persistent low growth profile (n=36)	12 (33%)	1.06 (0.42-2.60)	0.90	1.34 (0.49-3.69)	0.57	-
B: Normative growth profile (n=53)	17 (32%)	[Reference]		[Reference]		-
C: Transient overweight profile (n=49)	22 (45%)	1.73 (0.77-3.91)	0.19	1.70 (0.69-4.17)	0.25	-
D: Late-onset overweight profile (n=26)	6 (23%)	0.64 (0.20-1.81)	0.41	0.56 (0.16-1.96)	0.36	-
E: Persistent obesity profile (n=4)	2 (50%)	2.12 (0.24-18.9)	0.47	4.60 (0.40-52.8)	0.22	-

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus; RV, rhinovirus

* Regression models with a complete case analysis excluding patients with missing outcome: 7 in profile A, 5 in profile B, 5 in profile C, 12 in profile D, and 2 in profile E among RSV infection; 2 in profile A, 4 in profile B, 0 in profile C, 3 in profile D, and 0 in profile E among rhinovirus infection

† Adjusted for sex, race/ethnicity, prematurity (32–36.9 weeks), history of eczema, cigarette smoke exposure at home, parental history of asthma, parental history of eczema, and allergic sensitization.

‡ The E-value (with its lower 95% CI bound) represents how strongly unmeasured confounder(s) would have to be associated with the exposure and outcome in order for the observed association to be independent.

Table E7. Unadjusted and adjusted associations of six growth trajectory profiles with development of asthma

Growth trajectory profile	Number of outcomes, n (%)	Unadjusted model*		Adjusted model*, †		E-value (CI limit) [‡]
		Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	
1 (n=160)	33 (21%)	0.76 (0.47-1.23)	0.27	0.74 (0.44-1.24)	0.25	-
2 (n=198)	54 (27%)	1.11 (0.72-1.72)	0.62	0.98 (0.61-1.57)	0.29	-
3 (n=232)	60 (26%)	[Reference]		[Reference]		-
4 (n=153)	40 (26%)	1.04 (0.65-1.66)	0.86	1.00 (0.61-1.64)	0.99	-
5 (n=112)	28 (25%)	0.99 (0.58-1.66)	0.37	1.03 (0.59- 1.79)	0.91	-
6 (n=25)	10 (40%)	2.13 (0.87-5.10)	0.09	2.62 (1.03- 6.68)	0.04	2.62 (1.13)

Abbreviation: CI, confidence interval

* Regression models with a complete case analysis excluding patients with missing outcome: 7 in profile 1, 10 in profile 2, 6 in profile 3, 7 in profile 4, 6 in profile 5, and 2 in profile 6.

† Adjusted for sex, race/ethnicity, prematurity (32–36.9 weeks), history of eczema, cigarette smoke exposure at home, parental history of asthma, and parental history of eczema, and allergic sensitization.

‡ The E-value (with its lower 95% CI bound) represents how strongly an unmeasured confounder would have to be associated with the exposure and outcome in order for the observed association to be independent.

Figure legends**Figure E1. Calinski-Harabasz index according to number of growth trajectory profiles**

The X axis indicates the number of growth trajectory profiles; the Y axis indicates the Calinski-Harabasz index value. Across the different numbers of growth trajectory profiles (from 3 to 8), the Calinski-Harabasz index was similar.

Figure E2. Alluvial plot to examine consistencies across different numbers of growth trajectory profiles

The X axis indicates the number of growth trajectory profiles (range 4-6); the Y axis indicates the count of infants. Each color band represents a group of infants with the original growth trajectory profiles (A-E). There are consistencies between the five original profiles (A-E) and four and six profiles.