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Associations of postnatal weight and length/height gain with wheeze, asthma and atopy: The PROBIT Study

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Abstract

Background—It has been hypothesised that postnatal weight and length/height gain are variously related to wheeze, asthma and atopy, however supporting evidence is limited and inconsistent.

Methods—Weights and lengths/heights of 12,171 term-infants were measured from birth to 12 months and at 6.5 years, and extracted from polyclinic records prospectively obtained between 12 and 60 months. Atopic phenotypes were ascertained at 6.5 years with the International Study of Asthma and Allergy in Childhood questionnaire and skin-prick tests. Logistic regression models investigated whether rates of weight and length/height gain from infancy to mid-childhood were associated with atopy phenotypes that have occurred ever or in the last 12 months.

Results—After controlling for confounders and prior weight and length/height gain, all weight gain variables except birthweight were positively associated with ever having wheezed ($p<0.1$). A one SD increase in weight gain rate between 0–3 months was associated with a 12% increase (2%–23%) in allergic rhinitis ever. No other consistent patterns of association were found for weight gain or length/height gain rate between 0–60 months with atopic outcomes at 6.5 years. In contrast, all atopy outcomes except for ever having asthma were associated with current weight and height, even after controlling for prior growth.

Conclusion—Current height and weight are more strongly associated with the development of atopic phenotypes in childhood than patterns of infant and early childhood growth, which may well reflect reverse causality (atopy effects on growth) or residual confounding by an unknown common cause of growth and atopy.

Keywords

wheeze; asthma; atopy; postnatal growth; weight gain; length gain

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INTRODUCTION

Prevalence rates and secular trends of asthma and atopy vary greatly between countries,[1–10] In Northern and Eastern Europe, asthma prevalence is reported to vary from 5.0% to 13.6%, and rhinoconjunctivtis from 2.0% to 13.0% among children aged 6–7 years,[11] Childhood asthma has been linked to increased doctor visits, school absenteeism and limited childhood activity,[12] whilst eczema and allergic rhinitis adversely affect quality of life. Identifying early-life risk factors for these diseases may present an opportunity for prevention.

A higher concordance of asthma and atopy in monozygotic than dizygotic twins implies a genetic component of the diseases,[13] but this cannot explain the steep increases in asthma/atopy rates observed in some regions,[12] or large variations in prevalence in genetically similar groups.[11] Low and high birth weight have been associated with asthma, [14];[15] and atopy,[16] but this association may be confounded by factors such as poverty and inner-city residence.[12] Research on growth and asthma/atopy has focused largely on associations with fetal growth,[17–19] and on steroid treatment with subsequent growth in childhood.[20–22] Little focus has been placed on associations of postnatal weight and length/height gain with asthma and atopy, and published studies are inconclusive with positive,[23–25] negative,[26];[27] and null associations reported.[28] Several studies to date have reported cross-sectional associations of weight with asthma in childhood.[29–33]

Between birth and 18 months of age there is a rapid increase in alveolar size and number and airway diameter continues to grow, so postnatal environmental influences have the potential to affect lung development.[24] We tested the hypothesis that weight and length/height gain between 0 and 60 months are associated with wheeze, asthma, allergic rhinitis, eczema and skin prick test results at 6.5 years, in a large contemporary cohort of term infants.

METHODS

Study population

The Promotion of Breastfeeding Intervention Trial (PROBIT) was a cluster randomised trial conducted in the Republic of Belarus, designed to investigate the effects of an intervention promoting prolonged and exclusive breastfeeding on infant and child health. Detailed methods have been previously reported.[34] Ethics approval was obtained from the Research Ethics Board of the Montreal Children's Hospital of the McGill University Health Centre. Participants were 17,046 mother-infant pairs, recruited between June 1996 and December 1997. To be eligible, neonates had to be full-term (≥ 37 weeks gestation), singleton, weigh at least 2500g, have an Apgar score ≥ 5 at 5 minutes, and have initiated breastfeeding.

At age 6.5 years, 13,889 (82%) children attended a follow-up research visit (PROBIT II). [35–39] Our study sample consists of 12,171 children who had complete data on all potential confounders, at least two measures of length/height and weight between birth and 60 months, weight and height at 6.5 years and at least one atopic outcome measure at 6.5 years.

Exposures and confounders

Study paediatricians measured infants' weights and lengths at scheduled clinic visits at 1, 2, 3, 6, 9 and 12 months. At the 6.5 year study visit, weights and lengths/heights of children measured at routine check-ups between 12 and 60 months were abstracted from medical records and weight and height measured using standardized techniques.[38] At the 6.5 year visit, parental height and weight were recorded by interviewing the child's accompanying parent. As only 2% of mothers reported smoking during pregnancy, this variable was not included in the main analyses, but was included in the confounder-adjusted models as a

sensitivity analysis. Exclusive breastfeeding at 3 months, mother's age, family history of atopy, parent's education and urban or rural residence were self-reported. Family history of atopy included 6 binary variables stating whether the mother, father or an older sibling had ever had asthma, hay fever or eczema. Parent's education was categorised as 'completed university', 'advanced secondary/partial university', 'common secondary' and 'incomplete secondary'. Study treatment arm was included in all confounder-adjusted models.

Outcomes

Atopy phenotypes were ascertained at the 6.5 year visit using the validated International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire, translated into Russian. [36] The outcomes (binary variables) are: wheeze ever, wheeze in the last 12 months, allergic rhinitis ever, allergic rhinitis in the last 12 months, eczema ever and asthma ever. Skin prick tests to five antigens were conducted (see online supplement for details): house dust mite, cat, birch pollen, mixed northern grasses, and Alternaria. A binary variable was constructed contrasting those who had no positive reaction to any of the antigens, with those who had a positive reaction to one or more of the antigens.

STATISTICAL ANALYSIS

Individual growth trajectories

Individual length/height and weight gain trajectories were estimated using a multi-level model, fitted using MLwiN version 2.16. For both genders, a multilevel model for length/height was fitted, with linear gain between 0 and 3 months, 3 and 12 months, 12 and 34 months and 34 and 60 months. An equivalent model was fitted for weight. This is a similar model to that which has been used before in this dataset, [40–42] but with the addition of the extra knot point at 34 months which was found during recent data updating. Using these models, length/height and weight at birth and parameters of growth between the defined knot points were estimated for each individual. These were then standardised (z-scored) by gender. Birth length/height and weight were further standardised by gestational age.[43]

Estimating associations between outcomes and weight and length/height gain rates

Logistic regression models allowing for clustering within clinics estimated associations of length/height and weight gain rates in from infancy to mid-childhood with all atopy phenotypes. Four models were fitted for each weight exposure: Model 1 adjusted for clustering by clinic only. Model 2 additionally adjusted for all potential confounders. Model 3 additionally included all preceding weight and length/height measurements. Similar models were fitted for length/height exposures, except that Model 2 additionally adjusted for birth weight, and model 3 only adjusted for preceding length/height, not weight. The independent effects of treatment arm allocation on asthma and other atopic outcomes in PROBIT have been reported previously.[36] Adjustment for the effect of the randomized treatment arm was achieved by including it as a covariate in all models. In secondary analyses, we examined mediation of these associations by weight and height at 6.5 years, mindful of the potential for collider bias (Model 4) [44]. Multivariable logistic models were fitted to examine associations of current weight and height at 6.5 years with all outcomes.

RESULTS

12,065 (99%) children had all six scheduled weight and length/height measures up to and including one year. The median number of routine weight and length/height measures between 1 year and the 6.5 year follow-up was 4 (min 0, max 6). 9772 (80.3%) children had all atopic outcome measures at 6.5 years and 12,167 (99.9%) had missing data for only one outcome or less. As shown in Table 1, differences in some characteristics were observed

between those participants included in our analysis compared to those excluded due to missing data; however, the magnitude of the differences for each of these characteristics was small. On average, length/height and weight velocity was greater in boys than in girls during the first 3 months, after which growth velocities were similar (Table 2). At 6.5 years, boys were taller and heavier than girls.

The fully adjusted models are presented in Tables 3, 4 and 5, and minimally adjusted and confounder adjusted models in Web tables A, B and C in the online supplement. There was no evidence of interaction between sex and each period of weight and length/height gain velocity with any of the outcomes (Web tables D and E), thus, we report models in which the sexes were combined are reported and sex is adjusted for in these models. As expected, the addition of maternal smoking during pregnancy to the confounder adjusted models did not alter any of our findings (Web tables F and G), and no independent effect of study treatment arm on atopic phenotypes was observed (Web table H).

Associations of weight gain velocities with atopy phenotypes

Overall, no consistent patterns of association were observed between weight gain rate and wheeze and asthma, or other atopy phenotypes in the fully adjusted model (Table 3). Weight gain velocity between 0 and 3 months and between 12 and 34 months was positively associated with ever having wheezed, and weight gain velocity between 0 and 3 months was positively associated with allergic rhinitis ever. Weight gain velocity from 12 to 34 months was inversely associated with skin prick test results, and weight gain velocity from 34 to 60 months was positively associated with skin prick test results. There was no evidence of associations of birth weight or weight gain rates in early childhood with wheeze in the last 12 months, asthma or eczema.

Associations of length/height gain velocities with atopy phenotypes

There were no consistent patterns of association between birth length or length/height gain rate and wheeze and asthma, or other atopy phenotypes in the fully adjusted model (Table 4). Length/height gain velocity between 12 and 34 months was positively associated with wheeze ever. Length/height gain velocity between 0 and 3 months was positively associated with allergic rhinitis ever. There were no associations of birth length or subsequent length/height gain velocity with wheeze and allergic rhinitis in the previous 12 months, asthma or eczema ever or skin prick test results.

Associations of current weight and height at 6.5 years with atopy phenotypes

There were positive associations of current weight, current height and current weight adjusted for current height with wheeze and allergic rhinitis (Table 5). There was evidence of a positive association of current weight adjusted for height with skin prick test results, and height at 6.5 years was negatively associated with ever having eczema

Mediation of associations between early weight and length/height gain and atopy phenotypes by current weight and height at 6.5 years

Associations of weight gain rates with ever having wheezed and ever having rhinitis were attenuated by the addition of weight and height at 6.5 years, but weight gain between 0 and 3 months remained positively associated with ever having wheeze, and weight gain rate between 12 and 60 months remained associated with skin prick test results (Model 4, Web Tables A and B).

DISCUSSION

Overall, no consistent patterns of association were found for weight and length/height gain rates from early-infancy to mid-childhood atopy phenotypes. There was evidence of an association of weight and length gain between 0 and 3 months with ever having allergic rhinitis, and evidence of an association of weight gain between 0 and 3 months, and length gain between 12 and 34 months with wheeze ever.

Associations of weight and height/length gain between 0 and 60 months with atopy phenotypes were consistent with those of current weight and height at 6.5 years with atopy phenotypes, but associations with current weight and height were larger in magnitude, even after controlling for previous growth. These results suggest that while current weight and/or height are associated with wheeze, eczema, allergic rhinitis and skin prick test results, the trajectory by which current size is reached is less relevant.

Strengths and limitations

Strengths of the analytical approach have been previously outlined. [45] Good follow-up rates and few differences between included and excluded participants make selection bias unlikely. We identified biological trajectories prior to analysis, rather than conducting analyses at multiple time points and then choosing *post hoc* to highlight those with the largest associations with atopy phenotypes. Our study sample was large, providing sufficient power to detect associations in outcome categories with the fewest cases such as wheeze and asthma in the last 12 months and other atopy phenotypes, and allowing us to test for an interaction by sex.

Several limitations to our study merit discussion. First, we must be cautious about inferring causality from observational analyses. We were unable to adjust for some potential confounders such as early viral infections and food allergies. Nevertheless, associations of weight and length/height gain with atopy phenotypes were only slightly attenuated after controlling for a number of potential key confounders, and the degree of attenuation (0–5%) suggests that residual confounding, although a theoretical possibility, probably does not fully explain the results.

Second, methods for measuring length/height and weight before age 6.5 years were not standardized, which could have increased measurement error and reduced the precision of our estimates. Such measurement error is likely to have been non-differential, however, and therefore should have attenuated associations towards the null.

Third, all children in the PROBIT trial weighed at least 2500g at birth, were born at term and initiated breastfeeding. Therefore our findings may not be generalisable to preterm infants or to formula-fed infants. [46];[47] Generalisability of our findings outside of Eastern Europe may also be limited, given the relatively low prevalence of atopy in Eastern European countries.[48];[49]

Fourth, all outcomes except for skin prick tests were self reported, although based on a widely used and validated questionnaire.[50] As wheeze is a common symptom of respiratory infection, reported wheeze categories are likely to include children with both transient and persistent wheezing. There are also limitations when diagnosing asthma, particularly in children. [51] [52] Consequently, reported asthma and wheeze categories are likely to be heterogeneous and potentially bias associations towards the null.

Fifth, we cannot rule out the possibility of reverse causality. Children whose parents answered ‘yes’ to questions enquiring about symptoms in the last 12 months may include

those who had symptoms first appear during this 12 month period, but also those who had symptoms before and throughout the 12 month period. Thus the weight and length/height gain exposures may not precede the occurrence of wheeze, asthma and atopic symptoms. The associations found between current weight and height and atopic outcomes may well be due to reverse causality (i.e. the development of asthma or atopy causing weight gain), as it seems unlikely that weight or height at 6.5 years could cause an atopic phenotypes that developed a few years earlier. Another potential explanation for these associations may be that there is residual confounding by an unknown common cause of both childhood growth trajectories and of atopy.

Comparison with other studies including term-infants

Prevalence of reported asthma in our study was relatively low at 1.2% compared to the ranges of asthma prevalences reported in other Northern and Eastern European countries (5.0–13.6%). However, the prevalence's of rhinitis ever (4.5%) and rhinitis is the last 12 months (3.2%) reported in our study are similar.[11] Findings from relevant studies regarding associations of childhood growth with asthma and other atopic outcomes have been inconclusive. In line with our findings, one relatively small study (n=197) reported no evidence of an association of early life weight gain (birth to 2/3years) with daily asthma symptoms, pulmonary function, and eczema during pre-school years,[28] and a larger study reported no evidence of associations for length/height gains between birth and 12 months with wheeze or atopy at 3 years.[23] As in our study, the likely non-homogeneity of the outcome groups may have weakened any associations between risk factors and outcomes, and power was limited due to small subgroup numbers (n≈150). Pike et al reported evidence of a positive association for greater weight gains between birth and12 months with atopic and non-atopic wheeze at age 3.[23] However, they highlighted that there were missing data for some confounding influences, notably maternal atopic status, meaning this association may be confounded. In line with our findings, accelerated weight gain from birth to 3 months following normal fetal growth has been associated with increased risks of asthma symptoms.[25] In a smaller study (n=131) higher rates of early infancy weight gain (5-14 weeks) were associated with impaired lung development, and in contrast, postnatal weight gain was not related to total respiratory compliance and only weakly related to $FEV_{0.4}$.[24] This suggests that particular aspects of growth may have differing effects on these components of lung development; however, chance may also explain these findings. In contrast to our findings, several studies have reported cross-sectional associations of weight with asthma.[29–33] However, in our study the prevalence of asthma was low which may, in part, explain the wide confidence intervals observed for the estimates of the association between current weight, height adjusted current weight and asthma. To our knowledge, no other studies have included postnatal weight or length/height gain as an exposure with allergic rhinitis as an outcome.

CONCLUSION

We found no evidence of consistent associations of infant to mid-childhood weight and length/height gain with atopy phenotypes, although there was weak evidence for an association of weight and length gain rate between 0–3 months with ever having allergic rhinitis and evidence of an association of weight gain rate between 0 and 3 months and length gain rate between 12 and 34 months with wheeze ever. Evidence of associations of current weight and/or height at 6.5 years with all atopy outcomes except for asthma ever, even after adjusting for previous growth velocity, suggests that current size is associated with wheeze and atopy, irrespective of the pattern or rate of preceding childhood weight and height/length growth, and this is likely to be due to reverse causality or residual confounding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Sample characteristics

	Participants included in our analysis				Excluded participants		
	Girls N = 5865	**Boys N = 6306**	**Total/combined N=12,171**	**N with data**	**Total combined N=4875**	**N with data**	**P**
Mothers' education							
Completed university	825 (14.07)	868 (13.76)	1693 (13.91)		137 (8.24)		
Advanced secondary/partial university	3045 (51.92)	3270 (51.86)	6315 (51.89)	12,171	750 (45.10)	1663	<0.001
Common secondary	1,803 (30.74)	1982 (31.43)	3785 (31.10)		644 (38.73)		
Incomplete secondary	192 (3.27)	186 (2.95)	378 (3.11)		132 (7.94)		
Mothers' anthropometry							
Weight, kg (SD)	66.41 (12.60)	66.27 (12.48)	66.34 (12.54)		65.32 (12.56)	1601	<0.01
Height, cm (SD)	164.47 (5.64)	164.30 (5.62)	164.38 (5.63)	12,171	164.46 (5.71)	1563	0.59
BMI, kg/m^2(SD)	24.53 (4.41)	24.53 (4.37)	24.53 (4.39)		23.85 (4.01)	1557	<0.001
Fathers' education							
Completed university	771 (13.15)	848 (13.45)	1619 (13.30)		100 (8.35)		
Advanced secondary/partial university	2797 (47.69)	2984 (47.32)	5781 (47.50)	12,171	572 (47.75)	1198	<0.001
Common secondary	2176 (37.10)	2339 (37.09)	4515 (37.10)		463 (38.65)		
Incomplete secondary	121 (2.06)	135 (2.14)	256 (2.10)		63 (5.26)		
Fathers' anthropometry							
Weight, kg (SD)	79.57 (11.50)	79.89 (11.37)	79.74 (11.43)		88.54 (12.86)	690	<0.001
Height, cm (SD)	175.97 (6.64)	176.12 (6.61)	176.05 (6.63)	12,171	176.31 (7.28)	366	0.46
BMI, kg/m^2(SD)	25.67 (3.26)	25.74 (3.27)	25.71 (3.26)		25.28 (3.20)	339	0.02
Outcomes at mean age 6.5 years							
Wheezed ever	487 (8.30)	771 (12.23)	1258 (10.34)	12,169	171 (10.11)	1691	0.08
Wheezed in the last 12 months	150 (2.56)	222 (3.52)	372 (3.06)	12,167	54 (3.19)	1691	0.76
Allergic rhinitis ever	231 (3.94)	313 (4.96)	544 (4.47)	12,169	97 (5.74)	1691	0.02
Allergic rhinitis in the last 12 months	165 (2.81)	221 (3.50)	386 (3.17)	12,171	68 (4.02)	1691	0.07
Eczema ever	56 (0.96)	66 (1.05)	122 (1.00)	12,159	19 (1.12)	1689	0.64
Asthma ever	54 (0.92)	87 (1.38)	141 (1.16)	12,171	24 (1.42)	1691	0.35
Positive skin prick test results	1036 (21.99)	1153 (22.72)	2189 (22.37)	9787	318 (23.63)	1346	0.30

	Participants included in our analysis				Excluded participants		
	Girls N = 5865	**Boys N = 6306**	**Total/combined N=12,171**	**N with data**	**Total combined N=4875**	**N with data**	**P**
Family history of atopy	182 (3.10)	190 (3.01)	372 (3.06)		176 (3.61)	4875	0.06
Urban residence	3,187 (54.34)	3,470 (55.03)	6657 (54.70)		3340 (68.51)	4875	<0.001
Treatment Arm	2966 (50.57)	3163 (50.16)	6129 (50.36)		2736 (56.12)	4875	<0.001
Maternal age (SD)	25.14 (4.90)	25.05 (4.86)	25.09 (4.88)		24.45 (5.00)	4874	<0.001
Exclusive Breastfeeding at 3 months	1593 (27.16)	1678 (26.61)	3271 (26.88)	12,171	1212 (24.86)	4875	<0.01
Mean Birth weight , kg (SD)	3.38 (0.40)	3.52 (0.42)	3.45 (0.42)		3.41 (0.42)	4875	<0.001
Mean Birthlength, cm (SD)	51.66 (2.05)	52.36 (2.18)	52.02 (2.15)		51.75 (2.12)	4875	<0.001
Mean weight at 6.5 years, kg(SD)	22.51 (3.65)	23.08 (3.58)	22.80 (3.62)		22.75 (3.59)	1657	0.55
Mean height at 6.5 years, cm (SD)	120.50 (5.24)	120.89 (5.13)	120.70 (5.18)		120.35 (5.14)	1656	<0.01

SD = standard deviation. P values for the differences between included and excluded participants were calculated using unpaired t-tests for continuous variables and chi-squared tests for categorical variables.

Table 2

Weight and length/height at birth and weight and length/height velocities from 3 months to 5 years from multilevel spline models for weight and length/height with age.

	Girls (N=5050)		Boys (N=5444)	
	Mean (SD)	**95% reference range**	**Mean (SD)**	**95% reference range**
Birth weight (kg)	3.33 (1.01)	1.48, 5.48	3.42 (1.00)	1.55, 5.46
0–3 month velocity (kg/year)	10.80 (0.99)	8.99, 12.94	11.89 (0.98)	10.17, 13.99
3–12 month velocity (kg/year)	6.10 (1.00)	4.26, 8.25	6.10 (1.00)	4.29, 8.28
12–34 month velocity (kg/year)	1.90 (1.05)	0.04, 4.34	1.90 (1.04)	0.06, 4.25
34–60 month velocity (kg/year)	2.11 (1.02)	0.30, 4.51	2.09 (1.01)	0.35, 4.39
Birthlength (cm)	51.42 (1.01)	49.62, 53.70	52.03 (1.00)	50.32, 54.18
0–3 month velocity (cm/year)	36.19 (0.99)	34.28, 38.17	38.57 (0.99)	36.59, 40.56
3–12 month velocity (cm/year)	20.51 (1.01)	18.53, 22.49	20.38 (1.01)	18.31, 22.28
12–34 month velocity (cm/year)	9.70 (1.04)	7.46, 11.86	9.70 (1.04)	7.50, 11.87
34–60 month velocity (cm/year)	7.40 (1.02)	5.27, 9.77	7.40 (1.02)	5.28, 9.48

Table 3

Associations of early-infancy to mid-childhood weight gain rate (gender adjusted z-score) with wheeze, eczema, allergic rhinitis and skin prick test results at 6.5 years, in the fully adjusted model †

	Birth weight			Growth 0–3 months			Growth 3–12 months			Growth 12–34 months			Growth 34–60 months		
Outcome	**OR[1]**	**95%CI**	**P**	**OR[2]**	**95%CI**	**P**	**OR[2]**	**95%CI**	**P**	**OR[2]**	**95%CI**	**P**	**OR[2]**	**95%CI**	**P**
Wheeze ever	1.02	(0.93,1.11)	0.73	1.12	(1.05,1.19)	<0.01	1.05	(0.99,1.12)	0.11	1.08	(1.01,1.15)	0.02	1.03	(0.94,1.13)	0.49
Wheeze in the last 12 months	1.13	(0.97,1.32)	0.11	1.06	(0.95,1.18)	0.28	1.07	(0.95,1.19)	0.26	1.08	(0.97,1.20)	0.16	0.93	(0.80,1.09)	0.37
Asthma ever	1.11	(0.88,1.40)	0.38	1.12	(0.95,1.32)	0.19	1.15	(0.96,1.36)	0.13	1.00	(0.84,1.18)	0.95	1.01	(0.80,1.28)	0.93
Allergic rhinitis ever	0.96	(0.85,1.10)	0.56	1.11	(1.02,1.22)	0.02	1.06	(0.97,1.17)	0.21	1.08	(0.99,1.18)	0.09	0.92	(0.80,1.05)	0.22
Allergic rhinitis in the last 12 months	0.97	(0.84,1.13)	0.74	1.10	(0.99,1.22)	0.06	1.10	(0.98,1.22)	0.10	1.06	(0.96,1.18)	0.25	0.95	(0.81,1.11)	0.51
Eczema ever	1.01	(0.78,1.31)	0.93	1.10	(0.92,1.32)	0.30	0.85	(0.70,1.04)	0.12	0.97	(0.80,1.18)	0.76	1.04	(0.78,1.38)	0.80
Positive skin prick test result	1.01	(0.93,1.09)	0.83	1.02	(0.96,1.08)	0.48	1.04	(0.98,1.10)	0.18	0.93	(0.88,0.99)	0.02	1.08	(1.00,1.17)	0.05

OR[1] = odds of outcome per z-score increase in birth weight

OR[2]= odds of outcome per z-score change in weight gain

†Adjusted for clustering by clinic; confounders: sex, treatment arm, exclusive breastfeeding at 3 months, parents' height and weight, mother's age, family history of atopy and parent's education and preceding weight and length/height

Table 4

Associations of early-infancy to mid-childhood length/height gain rate (gender adjusted z-score) with wheeze, eczema, allergic rhinitis and skin prick test results at 6.5 years, in the fully adjusted model †

	Birth length			Growth 0–3 months			Growth 3–12 months			Growth 12–34 months			Growth 34–60 months		
Outcome	**OR[1]**	**95%CI**	**P**	**OR[2]**	**95%CI**	**P**	**OR[2]**	**95%CI**	**P**	**OR[2]**	**95%CI**	**P**	**OR[2]**	**95%CI**	**P**
Wheeze ever	0.97	(0.89,1.07)	0.57	0.99	(0.92,1.06)	0.75	0.98	(0.91,1.05)	0.49	1.08	(1.01,1.15)	0.03	1.05	(0.98,1.12)	0.19
Wheeze in the last 12 months	0.90	(0.77,1.06)	0.21	1.08	(0.96,1.22)	0.19	0.99	(0.88,1.13)	0.93	0.96	(0.85,1.07)	0.46	1.02	(0.90,1.14)	0.78
Asthma ever	1.07	(0.84,1.37)	0.56	1.00	(0.82,1.21)	0.99	1.07	(0.87,1.30)	0.53	0.97	(0.81,1.16)	0.75	0.92	(0.77,1.11)	0.38
Allergic rhinitis ever	1.07	(0.94,1.23)	0.31	1.11	(1.01,1.23)	0.04	1.05	(0.95,1.17)	0.32	1.04	(0.94,1.14)	0.46	0.94	(0.85,1.04)	0.26
Allergic rhinitis in the last 12 months	1.05	(0.90,1.23)	0.54	1.10	(0.98,1.24)	0.12	1.03	(0.91,1.16)	0.63	1.08	(0.96,1.20)	0.20	0.91	(0.81,1.03)	0.15
Eczema ever	1.09	(0.83,1.42)	0.55	0.96	(0.78,1.18)	0.66	0.92	(0.74,1.13)	0.41	1.08	(0.89,1.32)	0.41	1.10	(0.90,1.36)	0.34
Positive skin prick test result	1.09	(0.83,1.42)	0.55	0.96	(0.78,1.18)	0.66	0.92	(0.74,1.13)	0.41	1.08	(0.89,1.32)	0.41	1.10	(0.90,1.36)	0.34

OR[1] = odds of outcome per z-score increase in birth length

OR[2]= odds of outcome per z-score change in length/height gain

†Adjusted for clustering by clinic; confounders: sex, treatment arm, exclusive breastfeeding at 3 months, parents' height and weight, mother's age, family history of atopy and parent's education; birth weight and preceding length/height measures.

Table 5

Associations of current weight and height (gender adjusted z-score) at 6.5 years with wheeze, eczema, allergic rhinitis and skin prick test results at 6.5 years, adjusted for clustering by clinic, confounders† and previous weight and height measurements

	Current weight[1]			Height adjusted current weight[2]			Current height[3]		
Outcome	**OR[2]**	**95%CI**	**P**	**OR[2]**	**95%CI**	**P**	**OR[2]**	**95%CI**	**P**
Wheeze ever	1.07	(0.99,1.16)	0.09	1.12	(1.01,1.23)	0.03	1.10	(1.01,1.19)	0.04
Wheeze in the last 12 months	1.15	(1.00,1.31)	0.05	1.16	(0.98,1.36)	0.07	1.16	(1.00,1.34)	0.06
Asthma ever	1.15	(0.92,1.42)	0.21	1.12	(0.86,1.46)	0.41	1.19	(0.93,1.51)	0.16
Allergic rhinitis ever	1.13	(1.01,1.26)	0.03	1.14	(0.99,1.31)	0.07	1.16	(1.02,1.32)	0.02
Allergic rhinitis in the last 12 months	1.14	(1.00,1.30)	0.06	1.16	(0.99,1.36)	0.07	1.17	(1.01,1.36)	0.04
Eczema ever	0.84	(0.65,1.09)	0.18	0.98	(0.72,1.35)	0.92	0.75	(0.59,0.97)	0.03
Positive skin prick test result	1.03	(0.95,1.11)	0.52	1.12	(1.02,1.23)	0.02	0.94	(0.87,1.02)	0.12

[1]Adjusted for clustering by clinic, confounders and all previous weight measurements

[2]Adjusted for clustering by clinic, current height, confounders and all previous weight and height measurements

[3]Adjusted for clustering by clinic, confounders and all previous height measurements and birthweight

†Adjusted for confounders: sex, age at outcome assessment, treatment arm, exclusive breastfeeding at 3 months, parents' height and weight, mothers' age, family history of atopy and parents' education