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Early childhood growth patterns and school-age respiratory resistance, fractional exhaled nitric oxide and asthma

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ABSTRACT

Background: Greater infant weight gain is associated with lower lung function and increased risk of childhood asthma. The role of early childhood peak growth patterns is unclear. We assessed the associations of individually derived early childhood peak growth patterns with respiratory resistance, fractional exhaled nitric oxide, wheezing patterns and asthma until school-age.

Methods: We performed a population-based prospective cohort study among 5,364 children. Repeated growth measurements between 0 and 3 years of age were used to derive standard deviation scores (SDS) of peak height and weight velocities, and body mass index and age at adiposity peak. Respiratory resistance and fractional exhaled nitric oxide were measured at 6 years of age. Wheezing patterns and asthma were prospectively assessed by annual questionnaires. We also assessed whether any association was explained by childhood weight status.

Results: Greater peak height velocity was associated with lower respiratory resistance [Z-score (95% CI): -0.03 (-0.04, -0.01) per SDS increase] (n=3,382). Greater peak weight velocity and body mass index at adiposity peak were associated with increased risks of early wheezing [Relative-Risk Ratio (95% CI): 1.11 (1.06, 1.16), 1.26 (1.11, 1.43), respectively] and persistent wheezing [Relative-Risk Ratio (95% CI): 1.09 (1.03, 1.16), 1.37 (1.17, 1.60), respectively] (n=3,189 and n=3,005, respectively). Childhood weight status partly explained these associations. No other associations were observed.

Conclusions: Peak weight velocity and body mass index at adiposity peak are critical for lung developmental and risk of school-age wheezing. Follow-up studies at older ages are needed to elucidate whether these effects persist at later ages.

Keywords: asthma, cohort study, growth, lung function

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INTRODUCTION

Greater infant weight gain is suggested to be associated with lower lung function and increased risk of asthma in childhood (1-3). Changes in early life growth patterns may lead to adaptations in airway and lung growth resulting in higher obstructive-related respiratory resistance and airway inflammation, and subsequently increased risk of asthma in later life (4). Previous studies, including ours (2, 3), suggest that the immediate postnatal developmental period might be the most critical period for growth affecting lung adaptations and risk of later asthma (2, 3, 5-17). Most of these studies defined weight gain as the

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difference between weight measurements taken at two time points. However, early childhood growth can be analyzed in more detail by constructing individual longitudinal growth curves from repeated anthropometric measures. These early childhood growth curves are typically characterized using measures of peak height and weight velocities (PHV and PWV, respectively) which occur at around 1 month of age, and body mass index (BMI) and age at adiposity peak (BMIAP and AGEAP, respectively) which usually occur at around 9 months (18, 19). Variations in these early childhood growth patterns have been associated with metabolic health and obesity in adult life (18, 19). However, a limited number of previous studies however, have used individual peak growth velocities in relation to childhood respiratory outcomes (11, 16, 17, 19, 20). They observed that PWV was associated with an increased risk of asthma up to age 10 (11, 16), and with reduced lung function at 15 years (17). PHV was not associated with any respiratory disorder (11, 16). None of these studies evaluated the association of BMIAP with childhood lung function and asthma and only one assessed the role of child's current weight status (16). Moreover, the majority of studies have used parental-reported asthma symptoms and/or spirometry as markers of respiratory function. Spirometry is the recommended technique to assess lung function but it is not easy to conduct in young healthy children who are not familiar with the technique (21). The respiratory resistance (Rint) technique is suitable for young children and can discriminate between different wheezing phenotypes and between healthy and asthmatic children (21). Finally, the diagnosis of asthma based on symptoms and lung function tests, does not always reflect the underlying airway inflammation associated with asthma. Fractional exhaled nitric oxide (FeNO) has been considered a validated non-invasive method for assessing asthma-related eosinophilic airway inflammation(22).

Therefore we examined, in a population-based prospective cohort, the associations of early childhood growth patterns with markers of respiratory function. These markers included

respiratory resistance (Rint), fractional exhaled nitric oxide (FeNO), and the risk of wheezing patterns and asthma until school-age. We additionally explored if any association could be explained by childhood weight status.

METHODS

Design The study was embedded within the Generation R Study, a population-based prospective cohort study of children and their parents from early fetal life onwards in Rotterdam, the Netherlands (23). The study has been approved by the Medical Ethical Committee of the Erasmus MC, University Medical Centre in Rotterdam (MEC-2007-413-NL21545.078). At age 6 years, a total of 5,364 children with available data on detailed early childhood growth patterns participated in measurements of Rint, FeNO, wheezing patterns, and asthma until school-age (**Figure S1**).

Longitudinal early childhood growth patterns As previously described (20), weight and length or height were measured by well-trained staff at the ages of 1, 2, 3, 4, 6, 11, 14, 18, 24, and 36 months based on the national care program in the Netherlands. Children were included if they had a minimum of 3 measurements; the median number of growth measurements was 5 (range: 3-8). PHV and PWV in early childhood were derived using the Reed1 model for boys and girls separately, as described previously (20) and summarized in the Supplementary Material. BMIAP and AGEAP were derived using a cubic mixed effects model fitted on log(BMI) from 14 days to 1.5 years, including sex as covariate (20). PHV, PWH, and BMIAP were expressed as standard deviation scores (SDS) whereas AGEAP was categorized into 7.2-8.4 months (reference), 8.5-9.0 months, and 9.1-10.8 months (**Figure S2**).

Childhood lung function and asthma At the age of 6 years, Rint and FeNO measurements were performed according to European Respiratory Society (ERS) and American Thoracic Society (ATS) recommendations (24). Rint was measured by interrupter resistance in kPa/L (MicroRint, MicroMedical, Rochester, Kent, UK) during tidal expiration, with occlusion of the airway at peak expiratory flow. Median values for at least 5 acceptable Rint measurements were calculated and converted into sex- and height-adjusted Z-scores (25). FeNO in ppb was measured using the NIOX Flex chemiluminescence analyser (Aerocrine AB, Solna, Sweden) (24). FeNO levels were natural log-transformed to obtain normality. Wheezing in the past 12 months was obtained by parental questionnaires, adapted from the International Study on Asthma and Allergy in Childhood (ISAAC) (26), at the ages of 1, 2, 3, 4 and 6 years. Wheezing patterns were based on four wheezing categories (27): (i) no wheezing; (ii) early wheezing, ≤ 3 years only; (iii) late wheezing, > 3 years only; and (iv) persistent wheezing, $\leq$ and > 3 years. We combined information on physician-diagnosed asthma ever obtained at 6 years with data on wheezing in the past 12 months at age 6 years into current asthma.

Covariates information Information on maternal characteristics, including age at enrolment, pre-pregnancy body mass index (BMI), educational level, history of asthma or atopy, pet keeping, psychological distress, parity, and smoking during pregnancy, was obtained from questionnaires during pregnancy. Maternal psychological distress was defined using the Global Severity Index (GSI) (28). Maternal gestational hypertensive disorders, gestational diabetes, and child's sex, gestational age and weight at birth were obtained from midwife and hospital records. Ethnicity was based on country of birth of the parents (29). Postnatal questionnaires provided information on breastfeeding, day-care attendance in the first year, and lower respiratory tract infections, inhalant allergies (house dust mite, pollen, pets), and television viewing as a proxy of child's physical activity. Length and weight at age 2 and 6

years were measured and BMI (in kg/m²) adjusted for age and sex was calculated. Selection of covariates to be included in the models was based on previous literature (2, 11, 15, 16, 20, 27) and whether they were associated with at least one exposure and one outcome ($P < 0.05$). We performed multiple imputation for missing values of covariates to reduce bias and increase power. Chained equations were used in which 10 completed datasets were generated and analyzed using the standard combination rules for multiple imputations (30). Distributions of covariates in the imputed dataset were similar to those observed (Table S1). No major differences in the magnitude or direction of the effect estimates were observed between analyses with imputed data and complete cases only; therefore, only the results based on imputed datasets were presented.

Statistical analysis We used generalized linear regression models to assess the associations of early growth patterns with Rint and FeNO. Associations of early growth patterns with wheezing patterns were assessed using multinomial logistic regression models, whereas associations with current asthma were assessed using logistic regression models. All models were adjusted for maternal age at enrolment, pre-pregnancy BMI, educational level, history of asthma or atopy, psychological distress, parity, smoking during pregnancy, and child's sex, gestational age, birth weight, ethnicity, breastfeeding, day care attendance, and age of the child at the time of respiratory outcomes (Supplementary Material). Potential mediation by lower respiratory tract infections, inhalant allergies, television viewing, and BMI at age 2 and 6 years was assessed by inclusion of these potential mediators in the models as covariates. If they changed the effect estimates coefficient more than 10% we additionally performed mediation analysis by the formula: $100 \times (\text{effect estimate}_{\text{mediator}} - \text{effect estimate}_{\text{model 1}}) / (\text{effect estimate}_{\text{model 1}} - 1)$. A 95% confidence intervals (CI) for the percentage change of the effect estimate was calculated using a bootstrap method with 1,000 resamplings (31, 32). Effect

estimates are presented in Z-scores differences for Rint measurements, Sympercents for FeNO measurements (symmetric percentage differences which reflect regression coefficients of log-transformed FeNO*100%) (33), Relative-Risks Ratio (RRRs) for wheezing or Odds Ratio (OR) for current asthma, with their 95% CI. All statistical analyses were conducted with Stata 12.0 statistical software (Stata Corporation, College Station, Texas). Mediation analysis was conducted with R software (34).

RESULTS

Characteristics of mothers and children are given in **Table 1**. Characteristics of mothers and children differed for those included and excluded from the different analyses, apart from maternal history of asthma or atopy, pet keeping, child's sex, and BMI at 2 years (**Table 1**).

A greater PHV was associated with a lower Rint (Z-score -0.03 [95% CI, -0.04 to -0.01], per SDS increase) (n=3,382) (**Table 2**). PWV, BMIAP, or AGEAP were not associated with Rint z-score. None of the early growth patterns were associated with FeNO (**Table 2**). A greater PWV and BMIAP were associated with increased risks of early wheezing (RRRs, 1.11 [95% CI, 1.06-1.16] and 1.26 [95% CI, 1.11-1.43], respectively, per SDS increase) (n= and persistent wheezing (RRRs, 1.09 [95% CI, 1.03, 1.16] and 1.37 [95% CI, 1.17, 1.60], respectively, per SDS increase) (n=3,189 and n=3,005, respectively) (**Figure 1**). Neither PHV nor AGEAP were associated with early, late or persistent wheezing patterns (**Figure 1**). We did not find evidence of associations between early growth patterns and current asthma (**Table 2**).

After including the potential mediators in the models, only the effect estimates of PWV and BMIAP with early and persistent wheezing changed more than 10% (**Table 3 and Table S3**) and hence, we only performed mediation analysis for these associations. Mediation analyses

revealed that childhood BMI at 2 years did not mediate the association of PWV with early wheezing but BMI at 2 and 6 years mediated the association of PWV with persistent wheezing by 32% (17%-48%) and 33% (25%-39%), respectively (**Table 3**). Regarding BMIAP, BMI at 2 years mediated the association with early wheezing by 33% (14%-57%) whereas BMI at 6 years, but not at earlier ages, mediated the association with persistent wheezing by 24% (13%-32%) (**Table 3**). Television viewing at 6 years mediated the association of BMIAP with persistent wheezing by only 1% (0%-2%) (**Table S2**). We did not observe any mediating effect of lower respiratory tract infections or inhalant allergies (**Table S2**).

DISCUSSION

Our results suggest that greater PHV was associated with lower respiratory resistance at age 6 years, and that greater PWV and BMIAP were associated with increased risk of early and persistent wheezing, respectively, at school-age. Childhood weight status partly explained these later associations. AGEAP was not associated with childhood Rint, FeNO, wheezing or asthma.

Of studies that examined the association of early growth with lung function, wheezing or asthma in childhood (2, 3, 5-17) only three have used individual peak growth velocities (11, 16, 17). However, none of them found associations of PHV with respiratory outcomes (11, 16), while we did with lower respiratory resistance at age 6 years. Two studies which used the difference between height measurements taken at two time points to define childhood height growth instead of PHV, did not find any association of height growth with lung function or wheezing symptoms at 5 years (12) or found that greater height growth was associated with lower lung function at 15 years (15). In these studies lung function was assessed using

spirometry. Differences in results with our study might be explained by differences in the height gain definition, the age at which lung function and asthma were measured, and method of lung function measurement.

Concerning PWV, the three previous studies that used individual peak growth velocities (11, 16, 17) found associations of greater PWV with lower flow indices measured by spirometry and with an increased risk of maternal reported physician-diagnosed asthma or maternal reported asthma symptoms up to age 10 (11, 16). In the present study, we observed similar results of PWV with wheezing, which attenuated into non-significant after considering childhood BMI, but not with lung function or asthma. We observed that children with a greater BMIAP had an increased risk of early and persistent wheezing in childhood, and that the age when this BMIAP occurs (AGEAP) was not associated with any respiratory outcome. To our knowledge, no study thus far has evaluated BMIAP and AGEAP in relation to lung function, wheezing and asthma in childhood. Although childhood BMI mediated part of these associations, we still observed an increased risk of persistent wheezing associated with greater BMIAP.

We observed that greater height gain reduces respiratory resistance most probably because airways, airway diameter, and lung volume are larger with greater height and hence lead to lower respiratory resistance. On the contrary, we observed that greater PWV and BMI were associated with increased risks of wheezing. Previous studies suggest that early weight growth, particularly from birth to 3 months of age (2, 12, 15), appear to be important for lung development. Our results suggest that weight growth during the first year of life, and not only until 3 months after birth (2, 12, 15), might be the most critical period for developmental lung adaptations and risk of school-age wheezing. Early childhood weight gain may directly affect

the asthma phenotype by mechanical effects including reduced lung and breathing volume, cytokine modulation via adipose tissue, changes in hormone levels such as leptin and adiponectin, through common genes or genetic regions, or through epigenetic modifications (4). In our study, we observed associations of these early weight gain parameters, particularly BMIAP, with wheezing patterns but not with Rint or FeNO. This suggests that other mechanisms rather than high respiratory resistance or eosinophilic airway inflammation might be responsible for wheezing. Wheezing, and especially early wheezing, may be partly caused by respiratory tract infections, mostly viral, or inhalant allergies, and this phenotype tends neither to be persistent nor to lead to asthma at later ages. This is in agreement with our results since the strongest effects for wheezing were seen for persistent rather than for early wheezing. We observed that BMI at the time of respiratory outcomes plays an important role in the associations of early childhood growth with persistent wheezing. This is understandable since both PWV and BMIAP have been associated with an increased risk of overweight/obesity and with adverse fat distribution profiles in later childhood (19, 20). Future studies need to consider childhood BMI when assessing these associations. In our population neither PWV nor BMIAP tended to increase the risk of asthma.

The major strength of this study relies on its prospective design and the large sample size. We used longitudinal growth curves to define height and weight gain fitted based on anthropometric measurements collected by well-trained staff at ten time points from birth to 3 years. We also took a large number of potential confounders and mediators into account.

However, some methodological aspects need to be addressed. First, children lost to follow-up more often had unfavourable growth and socioeconomic characteristics (**Tables 1 and S2**).

This could have led to biased effect estimates if the associations between growth patterns and respiratory outcomes would differ between subjects included and excluded from the analysis.

This seems unlikely but cannot be excluded. However, we should consider that our results may not be generalisable to the general population.. Second, wheezing and asthma were self-reported and therefore outcome misclassification cannot be ruled out due to under- or over-reporting of wheezing and asthma. This may have led to either attenuation or overestimation of the effect estimates. Finally, the traditional approach to mediation analysis may be subject to potential bias due to non-adjustment for mediator-outcome confounders or exposure-mediator interaction, among others, giving incorrect associations (35).

In conclusion, our study suggests that greater PHV in early infancy was associated with lower respiratory resistance, and that greater PWV and BMIAP with increased risk of early and persistent wheezing, respectively, at school-age. Childhood weight status partly explained these later associations. Previous studies showed that greater weight and height growth during infancy could be associated with increased risk of later respiratory outcomes, and our results suggest that specifically, PWV and BMI at adiposity peak, has a more critical role for lung development and risk of school-age wheezing. Follow-up studies at older ages are needed to elucidate whether these effects persist at later ages.

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TABLES AND FIGURES

Table 1 Difference in characteristics between subjects included and not included in the study

	Not included n = 2,940	Included n = 5,364			
		Rint available n = 3,480	FeNO available n = 3,177	Wheezing available n = 3,190	Current asthma available n = 4,085
Maternal characteristics					
Age at enrolment (years)	28.8 (5.6)	31.0 (4.9)*	31.1 (4.9)*	31.9 (4.3)*	31.7 (4.5)*
Pre-pregnancy body mass index (kg/m ²)	25.4 (4.8)	24.5 (4.2)*	24.4 (4.2)*	24.2 (4.0)*	24.3 (4.0)*
Educational level					
Primary or secondary	72.3	47.4*	45.5*	37.2*	40.8*
Higher	27.7	52.6	54.6	62.9	59.2
History of asthma or atopy, yes	35.3	36.9	36.4	37.9	36.6
Pet keeping, yes	34.0	32.5	33.1	34.2	33.4
Psychological distress, yes	14.7	7.7*	7.4*	4.9*	5.7*
Parity, multiparous	47.5	43.7	42.1*	39.6*	41.1*
Smoked during pregnancy, yes	31.2	23.9*	23.3	21.0*	21.3*
Gestational hypertensive disorders, yes	4.2	4.0	4.0	4.9*	4.4
Gestational diabetes, yes	1.9	0.7*	0.7*	0.7	0.7*

Infant characteristics

Sex, female	48.5	50.5	50.4	49.9	50.4
Gestational age (weeks) ¹	39.9 (26.3-43.6)	40.1 (26.7-43.4)*	40.1 (27.1-43.4)*	40.1 (25.3-43.4)*	40.1 (25.3-43.4)*
Birth weight (g)	3,292 (617)	3,451 (546)*	3,466 (530)*	3,478 (540)*	3,470 (551)*
Ethnicity, non-European	47.0	30.0*	28.2	19.3*	22.8*
Breastfeeding					
Never	14.3	8.9*	9.4	8.4*	9.0*
Partial until 4 months	68.9	64.8	64.6	62.6	63.8
Exclusive until 4 months	16.9	26.4	26.1	29.0	27.3
Day care attendance age 1 year, yes	43.0	61.0*	62.3*	65.2*	63.6*

Child characteristics

Lower respiratory tract infections, yes	6.2	4.9	4.6	4.4	4.1*
Inhalant allergies, yes	12.6	10.6	9.8	10.2	9.8*
Television viewing					
<2 hours/day	71.8	83.2*	84.5*	87.0*	85.2*
≥2 hours/day	28.2	16.8	15.5	13.0	14.8
Body mass index age 2 years (kg/m ²)	0.2 (1.1)	0.3 (1.0)	0.3 (1.0)	0.3 (1.0)	0.3 (1.0)
Body mass index age 6 years (kg/m ²)	0.4 (1.0)	0.3 (0.9)	0.2 (0.9)*	0.2 (0.8)*	0.2 (0.9)*

Values are percentages for categorical variables and means (SD) or median (range)¹ for continuous variables. Non-imputed data. *P*-value (included vs. not included) was estimated by using One-Way Anova, Wilcoxon, or Chi-square tests. **P*-value of differences between included and not included in each population <0.01.

Table 2 Association of early childhood growth patterns with respiratory resistance, fractional exhaled nitric oxide, and current asthma

	Rint		FeNO		Current asthma	
	n	Z-score (95% CI)	n	Sympercent (95% CI)	n	Odds Ratio (95% CI)
PHV	3,382	-0.03 (-0.04, -0.01)**	3,097	0.21 (-0.09, 0.51)	3,995	0.99 (0.97, 1.02)
PWV	3,471	-0.04 (-0.09, 0.02)	3,175	0.85 (-0.35, 2.05)	4,083	1.02 (0.93, 1.12)
BMIAP	3,173	0.09 (-0.06, 0.24)	2,915	0.70 (-2.55, 3.95)	3,787	1.01 (0.78, 1.30)
AGEAP						
7.2-8.4 months	1,983	reference	1,805	reference	2,309	reference
8.5-9.0 months	942	-0.07 (-0.32, 0.18)	885	-1.78 (-6.93, 3.37)	1,161	1.13 (0.75, 1.71)

		0.17)		3.36)		
9.1-10.8 months	248	0.10 (-0.31, 0.51)	225	-6.06 (-14.91, 2.79)	317	1.05 (0.52, 2.10)

Definition of abbreviations: PHV = peak height velocity; PWV = peak weight velocity; BMIAP = body mass index at adiposity peak; AGEAP = age at adiposity peak; Rint = respiratory resistance; FeNO = fractional exhaled nitric oxide. Values represent changes in Z-scores of Rint, Sympercents of FeNO(33), or odds ratios for asthma (compared with never asthma) with their 95% confidence intervals (CI) per standard deviation score (SDS) increase of early growth patterns or age at adiposity peak categories, and were obtained from linear or logistic regression models. One SDS of PHV equals 8.4 cm/year, of PWV 2.1 kg/year, and of BMIAP 0.8 kg/m². **P-value <0.01. Models were adjusted for maternal age at enrolment, pre-pregnancy BMI, educational level, history of asthma or atopy, psychological distress, parity, smoking during pregnancy, and child's sex, gestational age, birth weight, ethnicity, breastfeeding, day care attendance, and age of the child at the time of respiratory outcomes.

Table 3 Mediation analysis showing associations of peak weight velocity and body mass index at adiposity peak with wheezing patterns considering body mass index of the child at ages 2 and 6 years

	Risk of childhood wheezing Relative-Risk Ratio (95% Confidence Interval)				
	Full model	Full model + BMI age 2 years	% change (95% CI)	Full model + BMI age 6 years	% change (95% CI)
PWV					
Never n = 1632	reference	reference	reference	reference	reference
Early n = 944	1.11 (1.06, 1.16)**	1.08 (1.03, 1.15)**	-21.0 (-35.7, 12.0)	NA	NA
Persistent n = 478	1.09 (1.03, 1.16)**	1.06 (0.99, 1.14)	-31.5 (-47.5, -16.5)	1.06 (1.00, 1.13)	-32.9 (-38.6, -25.1)
BMIAP					
Never n = 1542	reference	reference	reference	reference	reference
Early n = 892	1.26 (1.11, 1.43)**	1.17 (0.98, 1.41)	-32.8 (-56.9, -13.6)	NA	NA
Persistent n = 441	1.37 (1.17, 1.60)**	1.33 (1.06, 1.66)*	-10.3 (-26.8, 12.7)	1.27 (1.06, 1.52)**	-24.2 (-31.6, -12.8)

Definition of abbreviations: PWV = peak weight velocity; BMIAP = body mass index a adiposity

peak; BMI = body mass index; NA = not applicable. Values represent changes in relative-risk ratios for wheezing patterns with their 95% confidence intervals (CI) per standard deviation score (SDS) increase of early growth patterns, and were obtained from multinomial logistic regression models. Potential mediators were included in our models if they were hypothesized to be within the causal pathway. Therefore, we additionally adjusted our models for BMI of the child at ages 2 and 6 years and calculated the percentage change of the effect estimate by the formula $100 \times (\text{effect estimate}_{\text{mediator}} - \text{effect estimate}_{\text{model 1}}) / (\text{effect estimate}_{\text{model 1}} - 1)$. A 95% CI for the percentage change of the effect estimate was calculated using a bootstrap method with 1,000 resamplings. One SDS of PWV equals 2.1 kg/year and of BMIAP 0.8 kg/m². *P-value <0.05. **P-value <0.01. Models were adjusted for maternal age at enrolment, pre-pregnancy BMI, educational level, history of asthma or atopy, psychological distress, parity, smoking during pregnancy, and child's sex, gestational age, birth weight, ethnicity, breastfeeding, day care attendance, and age of the child at the time of respiratory outcomes.

Figure 1 Association of early childhood growth patterns with wheezing patterns

Values represent relative-risk ratios for wheezing patterns with their 95% confidence intervals (CI) per standard deviation score (SDS) increase of early growth patterns or age at adiposity peak categories (reference: 7.2-8.4 months), and were obtained from multinomial logistic regression models. One SDS of peak height velocity equals 8.4 cm/year, of peak weight velocity 2.1 kg/year, and of body mass index at adiposity peak 0.8 kg/m². **P-value <0.01. Models were adjusted for maternal age at enrolment, pre-pregnancy BMI, educational level, history of asthma or atopy, psychological distress, parity, smoking during pregnancy, and child's sex, gestational age, birth weight, ethnicity, breastfeeding, day care attendance, and age of the child at the time of respiratory outcomes.

