



Infantile growth velocity and later asthma/wheeze: GENESIS and the Healthy Growth Study

To the Editor:

Accumulating evidence suggests that wheezing illnesses have at least part of their origin in the infantile period, wherein septal restructuring and alveolar formation ensue. Therefore, throughout infancy, genetic and environmental factors could affect bronchial development and future airway function. On this basis, we hypothesised that differential growth velocity, within the first 6 months of life, could be diversely linked to paediatric wheezing illnesses. Establishing such an interaction still eludes us, due to limited and conflicting evidence [1–6] and age-specific differences in bronchial function/structure [3]. We, therefore, opted to investigate a potential correlation in two populations of children of different ages, the Growth, Exercise and Nutrition Epidemiological Study In preSchoolers (GENESIS) study and the Healthy Growth Study cohorts (preschool and late childhood, respectively); thereby, we also appraised any age-definable discrepancies. These cross-sectional studies involved children aged 2–5 years attending nurseries in five Greek counties (GENESIS study) [7] and children aged 9–13 years, attending primary schools in four Greek counties (Healthy Growth Study) [8]. Sampling of nurseries/schools was stratified by parents' educational level and total student population in the respective municipality and their selection was random, as previously described [7, 8]. By using the parents' educational level as a proxy for socioeconomic level (SEL), we opted to compile a sample that was largely representative of the SEL level of Greek children. Specifically, municipalities were classified in three categories of different SELs *i.e.* Higher, Medium and Lower (Census 2001 [9]). Subsequently, certain municipalities were randomly selected from each one of these three SEL groups; their number was proportional to the size of each group's preschool/pre-adolescent population. Finally, schools were randomly selected from each municipality; their number was proportional to the municipality's schoolchildren population. Parental consent was acquired and the studies were approved by the Greek Ministry of Education and the Ethics Committee of the Harokopio University, Athens, Greece. Socio-demographic and perinatal data was collected and body fat assessment/anthropometric measurements were conducted during school interviews. The parents provided the researchers with their children's health books wherein (as part of standard practice in Greece) data from routine paediatrician-conducted measurements of infantile weight and length were recorded; this information was used to estimate weight-for-length z-scores based on the World Health Organization (WHO) growth charts. The z-score difference between birth and 6 months of age was used to classify children into the following categories: retarded growth velocity (≤ 1 z-score difference), normal growth velocity ($-1 \leq 1$ z-score difference), and rapid growth velocity (> 1 z-score difference). Potential atopic predisposition of the GENESIS participants was evaluated through the question: "Did a doctor ever tell you that your child has atopic dermatitis?". Asthma outcomes were defined from the International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaire. 1) Current wheeze (did your child have wheezing or whistling in the chest in the past 12 months?). 2) Ever wheeze (did your child have wheezing or whistling in the chest at any point in time?). 3) Asthma ever (did your child ever have asthma diagnosed by a doctor?). Complete data were available from 1668 children in the GENESIS study and 1867 children in the Healthy Growth Study. Univariate logistic regression analyses were conducted and followed by multivariate logistic regression analyses, whereby we adjusted for a wide array of potential confounding/intervening variables (table 1). The statistical package for social sciences (SPSS; IBM Corporation, Armonk, NY, USA), version 20.0 was used and a two-tailed $p < 0.05$ was considered significant.

The correlations uncovered by the univariate analyses were not meaningfully altered following the incorporation of the confounders in the models. Table 1 presents the unadjusted and adjusted associations of the infantile growth patterns with the main outcomes. In preschool children, rapid growth velocity in the first 6 months of life was positively associated with ever wheeze ($p = 0.005$) and asthma ever ($p = 0.036$) but not with current wheeze, following adjustment. In preadolescents, neither rapid nor retarded growth velocity was associated with any outcome ($p > 0.05$). Current wheeze did not correlate to any infantile growth pattern, in either population.

TABLE 1 Associations between infantile growth patterns (0–6 months) and main study outcomes in preschool children (GENESIS study) and pre-adolescent children (Healthy Growth Study)

| | Subjects | Yes for current wheeze | | | Yes for ever wheeze | | | Yes for physician-diagnosed asthma ever | | | |
|------------------------------|-----------|------------------------|------------|------------------|---------------------|-------------------------|--------------|---|--------------|-------------------------|--------------|
| | | Unadjusted | | Adjusted | Unadjusted | | Adjusted | Unadjusted | | Adjusted | |
| | | OR (95% CI) | p-value | OR (95% CI) | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | |
| GENESIS# | 1668 | 449 (27) | 611 (36.6) | 164 (9.8) | | | | | | | |
| Growth velocity | | | | | | | | | | | |
| Normal | 573 (35) | | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | |
| Retarded | 324 (19) | 0.92 (0.67–1.26) | 0.624 | 0.95 (0.69–1.32) | 0.782 | 1.26 (0.94–1.67) | 0.112 | 1.27 (0.95–1.71) | 0.104 | 0.93 (0.56–1.60) | 0.852 |
| Rapid | 771 (46) | 1.12 (0.87–1.42) | 0.366 | 1.15 (0.89–1.45) | 0.266 | 1.39 (1.11–1.74) | 0.005 | 1.40 (1.11–1.78) | 0.004 | 1.51 (1.04–2.19) | 0.027 |
| Healthy Growth Study* | 1867 | 65 (3.5) | 230 (12.3) | 247 (13.2) | | | | | | | |
| Growth velocity | | | | | | | | | | | |
| Normal | 1050 (56) | | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | |
| Retarded | 197 (11) | 1.95 (0.93–4.08) | 0.076 | 1.78 (0.83–3.8) | 0.138 | 1.11 (0.70–1.76) | 0.640 | 1.13 (0.71–1.79) | 0.600 | 1.38 (0.91–2.10) | 0.123 |
| Rapid | 620 (33) | 1.66 (0.97–2.84) | 0.064 | 1.54 (0.87–2.74) | 0.137 | 1.20 (0.89–1.62) | 0.224 | 1.11 (0.80–1.53) | 0.523 | 1.03 (0.77–1.39) | 0.814 |

Data are presented as n or n [%] unless otherwise stated. Adjusted for maternal age at birth, maternal prenatal smoking, gestational age, birth weight, sex, parity, breastfeeding (any time of exclusive breastfeeding versus formula only versus any time of mixed feeding), parental educational level, passive smoking at home, body mass index, waist circumference, sum of skinfold thickness (biceps, triceps, subscapular and suprailiac), for both studies. The GENESIS participants were also adjusted for parental-reported atopic dermatitis. Bold represents statistically significant correlations. GENESIS: Growth, Exercise and Nutrition Epidemiological Study in preSchoolers. # : children aged 2–5 years; * : children aged 9–13 years.

Investigations into infantile growth patterns were kindled by the “Barker” hypothesis, which maintains that retarded growth *in utero* could cause rapid infantile catch-up (compensatory) growth and have detrimental repercussions on later health. Notwithstanding a potential deleterious effect of intrauterine growth restraint *per se* on later asthma/wheeze, catch-up postnatal growth may instead be the main culprit. Although such mechanisms are not yet clear, they conceivably rely on a potential “programming”, whereby various infantile exposures including early-life growth could exert long-term effects on tissue function and dictate emergence of relevant pathology.

Pertinent evidence regarding asthma is limited, as only recently a potential infantile growth velocity/asthma relation has attracted attention. Investigators have reported a positive correlation of rapid infantile weight gain with wheeze at the age of 1, 3 and 4 years [1, 3, 10], with asthma up to the age of 10 years [4, 11], with preschool asthma exacerbations [2], and with adult wheeze [5]. In a recent report in the *European Respiratory Journal*, VAN DER GUGTEN *et al.* [6] showed that rapid infantile growth velocity is a risk factor for asthma/decreased lung function, up to the age of 5 years. This evidence is in keeping with our own findings of a positive association of rapid infantile growth velocity with ever wheeze and asthma incidence in preschool children. However, it is at odds with our findings in preadolescents, as in this age range we failed to show any such correlation. Age-specific variability in wheeze causation could partly reconcile these discrepancies. For instance, post-viral wheeze is prevalent in preschool children, whereas atopic wheeze is predominant in older children; hence, since rapid growth velocity was associated with asthma/wheeze only in the preschool age, it stands to reason that it may be linked to post-viral wheeze. Indeed, adjustment for atopic dermatitis in preschool children did not alter these correlations, suggesting that atopy does not perturb in this mechanism. In fact, infantile rapid growth velocity may act as a proxy for a predisposition to illness (and hence to post-illness wheeze), as it could compensate for the deceleration caused by illnesses during infancy [4]. This could also explain the lack of an association of rapid growth velocity with preschool current wheeze: ever wheeze (which was linked with rapid growth velocity in this cohort), could be predominant in infancy (due to infantile illness), rather than be current. Such mechanisms merit further research through prospective studies.

Our study’s strengths include its population-based design, findings from two discrete cohorts of children of different ages and control for several confounders. We adjusted for short gestational age and low birth weight, both of which are associated with asthma [10]. Low birth weight could also act as a surrogate for retarded fetal growth; hence, making allowance for it, minimises the possibility that the associations we reported were mediated by prenatal growth restraint [1, 10]. We also adjusted for current fat mass indices: body mass index, waist circumference and sum of skinfold thickness; insofar as accelerated infantile growth could be a risk factor for later obesity, controlling for them refutes the possibility that our findings are underpinned by an asthma-facilitating effect of excess fat mass. We further controlled for maternal prenatal smoking, a risk factor for fetal growth retardation [10] and preschool wheeze, in addition to maternal age at birth, passive smoking at home, parity, sex, breastfeeding and parental educational level, all of which modify asthma risk. Nevertheless, the retrospective design imposes certain limitations, such as potential recall and misclassification bias. Furthermore, atopy was not adjusted for through objective means, but rather through doctor-diagnosed atopic dermatitis, which is only one of many possible marks of an atopic phenotype. However, in light of the well-established temporal course of the atopic march, we feel that skin manifestations are a relevant marker of atopy for a preschool-aged cohort. In any case, an association of infantile growth patterns with atopy *per se*, has been contested in several studies [1, 3, 5, 10].

In conclusion, we report that rapid growth velocity in the first 6 months of life is linked to increased wheeze and asthma incidence in preschool children but not preadolescents. Importantly, this correlation is independent of current fat mass and birth weight, suggesting that it is unrelated to obesity and *in utero* growth retardation, respectively. Confinement of this association in the preschool age and lack of interference of atopy, imply a link of rapid growth velocity with post-viral wheeze. We believe that further research into these mechanisms could have important implications in preschool-wheeze prevention.



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Rapid infantile growth velocity: positively associated with later wheeze/asthma in preschoolers not pre-adolescents <http://ow.ly/sZ3Pr>

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