


ORIGINAL ARTICLE

Epidemiology of Allergic Disease

Increased risk of asthma in overweight children born large for gestational age

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Summary

Background: Being born large for gestational age (LGA) is a marker of increased growth velocity in fetal life and a risk factor for childhood overweight. Both being born LGA and childhood overweight may influence the development of asthma, although the role of overweight in the association between LGA and childhood asthma is unclear. Importantly, recent studies have suggested that the association between overweight and asthma may be related to non-allergic pathways. If this also applies to the association between LGA and asthma, the association between being born LGA and asthma may be different for atopic and non-atopic children.

Objective: We investigated the association of being LGA with the prevalence of asthma at age 8 in atopic and non-atopic children and the role of overweight in this association.

Methods: Complete data on asthma, anthropometry and atopy at age of 8 years, and potential confounders were available for 1608 participants of the PIAMA birth cohort. Odds ratios for the association between LGA and asthma in atopic and non-atopic children were estimated by logistic regression analysis adjusting for potential confounders. Overweight was assessed as a potential modifier of the association between LGA and asthma.

Results: Being born LGA was not significantly associated with asthma at age of 8 in atopic and non-atopic children. However, overweight at age of 8 years modified the association between asthma at age of 8 and LGA. In non-atopic children, children

who were born LGA and were overweight at age of 8 years had a significantly increased odds of asthma compared to non-LGA, non-overweight children (adj OR 7.04; 95% CI 2.2-24).

Conclusions: We observed that non-atopic children born LGA, who were overweight by 8 years have an increased risk of asthma. If confirmed, these findings suggest that non-atopic children born LGA may be identified early in life as a high-risk group for asthma.

KEYWORDS

asthma, epidemiology, overweight, paediatrics

1 | INTRODUCTION

The adverse effects of low birth weight on long-term health outcomes have been documented extensively, but more recently it has been observed that also a high birthweight is associated with an increased risk of type 2 diabetes and overweight.^{1,2} Being large for gestational age (LGA definition: >90th percentile at birth) is a marker of increased growth velocity in fetal life³ and children who are born LGA run a higher risk of overweight⁴⁻⁷ and possibly asthma.⁸⁻¹⁰ Overweight as such is an independent and relevant risk factor for childhood asthma,^{11,12} but its role in the association between LGA and asthma is unclear. Moreover, overweight is more strongly associated with asthma in non-atopic than in atopic children,^{13,14} and this may also apply to the association between LGA and asthma. Classic atopic asthma is predominantly associated with allergic inflammation with a relative bias towards a type 2 T-helper cell (Th2) response.¹⁵ However, the proportion of asthma attributable to atopy in school age children has been estimated to be only 31.6%.¹⁶ The non-atopic phenotype is the most common presentation of childhood asthma in some Latin American population samples.^{17,18} Although atopy is associated with asthma, a significant proportion of childhood asthma can occur among non-atopic children. Thus, it is relevant to investigate the effect of LGA on asthma separately in atopic and non-atopic children and to consider the role of overweight in this association.

The aim of this study was to investigate the association of being LGA at birth with having asthma at age of 8 years in atopic and non-atopic children who were participants in the PIAMA birth cohort. We also investigated the role of overweight at age of 8 in this association.

2 | MATERIALS AND METHODS

2.1 | Study population

The children in this study were participants in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study and were born in 1996-1997. The study protocol was approved by the medical ethics committees of the participating institutes

(protocol age 8 years: Utrecht METC approval number 04-101/K; Rotterdam P04.0071C/MEC 2004-152; Groningen P04.0071C/M4.019912), and all parents gave written informed consent. Detailed descriptions of the study design have been published previously.^{19,20} At baseline, the cohort consisted of 4146 pregnant women, 183 being lost to follow-up before any data of the child had been collected, so that the study started with 3963 newborns (Figure 1).

At the age of 8 years, 3653 children (92.2%) were still in the study. Parents of 135 children indicated in questionnaires before the age of 8 years that their child would not be eligible for participation in the clinical examination for practical or personal reasons, but that they would stay in the study for the questionnaire part only. These children were not re-invited for the clinical examination at 8 years. Thus, 3518 children were invited to come to one of the university hospitals or a community health centre for a clinical examination including anthropometric measurements and blood sampling. Children from allergic mothers were all invited to be seen in the hospital settings allowing additional clinical tests (such as bronchial hyperresponsiveness) for other research purposes. Due to differences in logistics in inviting to hospitals and community health centres, the response of children from allergic mothers was higher than the response of those from non-allergic mothers, leading to an overrepresentation of children from allergic mothers in the study population. For that reason, maternal allergy was taken into account in all statistical analyses. A total of 2214 children (63% of invited children) participated in the clinical examination. Anthropometry data and specific IgE concentrations were available for 1697 children. After exclusion of children with missing information on gestational age, birthweight and asthma at age of 8 years the final study population for this analysis consisted of 1608 children.

2.2 | Definition of variables

The main exposure variable was LGA. Birthweight was obtained from the parents from the child's delivery chart and reported in the 3-month questionnaire. Being LGA was defined as birthweight higher than 90% percentile for sex, gestational age and parity, considering the Dutch reference values.²¹

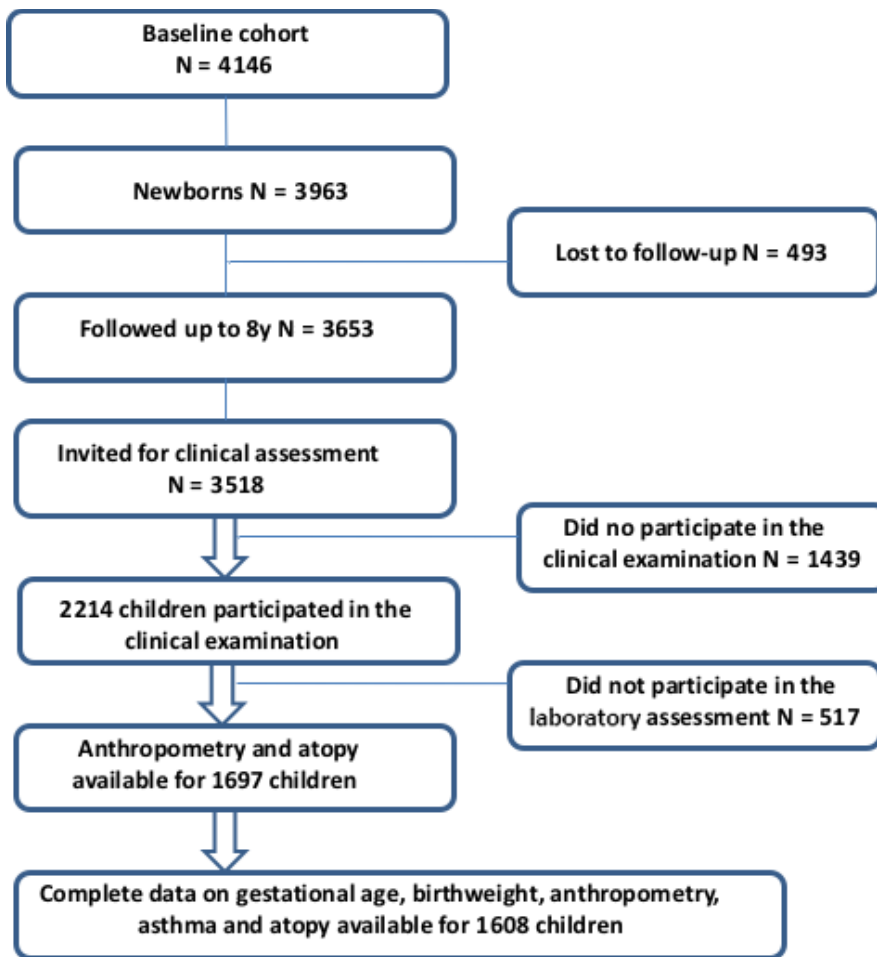


FIGURE 1 Flow chart of study population describing how subjects from PIAMA cohort were included in the analysis (children with complete anthropometric data and complete data on atopic sensitization at 8 y)

The outcome in our study is the prevalence of asthma at 8 years of age in the total study population of 1608 children and in strata of atopic and non-atopic children. The following three questionnaire items have been used for the case definition of asthma: (1) at least one episode of wheezing in the last 12 months; (2) asthma medications prescribed by a medical doctor in the last 12 months; and (3) a parental report of a doctor's diagnosis of asthma ever. In the analyses, asthma was defined as at least two positive answers to these items at age of 8 years.¹⁶ This definition has been developed by a panel of experts within the MeDALL consortium.¹⁶ Atopy was defined as having a specific IgE concentration >0.35 IU/ml against one or more of the following allergens: house dust mite, cat, dog, grass, birch pollen, *Alternaria alternata*, milk or egg.

Overweight was considered as a potential modifier of the association between LGA and asthma. The child's weight and height have been measured during the 8-year clinical examination and used to calculate the child's body mass index (BMI). BMI is not a gold standard indicator of adiposity, but as it reflects high weight for height, it is widely accepted as a proxy for overweight. The age- and sex-specific cut-off points of the International Obesity Task Force for BMI were used to define overweight at 8 years of age.^{22,23} Throughout the paper, we use the term "overweight" for children with a BMI above the cut-off point for overweight. Thus, the term "overweight" includes moderate overweight as well as obesity.

Potential confounders that were considered *a priori* were selected based on findings from previous epidemiological studies and available knowledge on asthma aetiology. In addition, we also investigated the potential confounding effect of characteristics that differed between study participants that were included ($n=1608$) and excluded ($n=2355$) from this analysis. These include sex, maternal smoking during pregnancy (smoking during at least the first 4 weeks of pregnancy), breastfeeding (>16 weeks), having been born in hospital (yes/no), having been born by caesarean section (yes/no), maternal educational level (low: primary school, lower vocational training or lower secondary education; intermediate: intermediate vocational education or intermediate/higher secondary education; high, higher vocational education or university degree) and maternal allergy (asthma ever and/or current house dust mite allergy and/or pet allergy and/or hayfever).

2.3 | Statistical analysis

Odds ratios (ORs) of the association between being born LGA and asthma at 8 years were estimated by logistic regression analysis for the total study population and for atopic and non-atopic children, separately.

To avoid biased reference groups, the analysis of the association between LGA and asthma at 8 years in atopic and non-atopic

children was performed separately in the two strata.²⁴ To investigate overweight as a potential modifier of the association between LGA and asthma, we created a LGA-overweight (LGA-OW) combinatorial variable and estimated the adjusted ORs for the three LGA-OW strata compared to the reference group of non-LGA, non-OW children. Potential effect modification by atopy and sex was assessed by stratification. Analyses were performed with SPSS 20.0 (IBM, New York, NY, USA).

3 | RESULTS

The study population for analysis (n=1608) consisted of 48.6% girls and 20.5% of the children had a mother with a low educational level. The prevalence of asthma at 8 years was 8.3% (15.2% in atopic children and 3.6% in non-atopic children). Children that were included in the analysis less often had mothers with a low educational level and maternal allergy, less often had perinatal smoke exposure and more often received breastfeeding >16 weeks (Table 1).

Frequency distributions of asthma for the four LGA-OW strata for the total population and atopic and non-atopic children, separately, are presented in Table 2. In children who were both born LGA and overweight at 8 years, we observed a statistically significant increased odds of asthma, as compared to children who had neither of these risk factors (OR: 2.8, 95% CI: 1.6-6.6, in the total population; and 6.4, 2.0-20 among non-atopic children) (Table 2).

After adjustment for potential confounders, we did not find an association between LGA and asthma at age of 8 in the total study

population. Likewise, there was no association in strata of atopic and non-atopic children (Table 3). However, when we looked at the combinations of LGA with overweight, we observed a significantly increased odds of asthma for children that were both LGA and overweight (adj. OR: 2.7; 95% CI: 1.1-6.4), in particular in the non-atopic children (adj. OR: 7.0; 95% CI: 2.0-24.4) (Table 3). In stratified analyses by sex, we did observe a significantly increased odds of asthma for children that were both LGA and overweight in girls, but not in boys (Table S1).

4 | DISCUSSION

The association between high birthweight and childhood asthma has been previously described.⁸⁻¹⁰ Our study expands the knowledge on this association by suggesting that being born LGA strongly increases the risk of asthma in the group of non-atopic children who are overweight at 8 years. Improving the knowledge on the association between LGA, overweight and asthma may be important for preventive interventions, considering that these are early life or modifiable risk factors.

The association between high birthweight or LGA and childhood overweight has been previously described.^{4,6,7} After birth, the growth of LGA infants generally slows down during the first months of life.²⁵ However, for children born LGA, there seems to be an increase in BMI after 3 years of age.²⁶

Also, previous studies have reported an association between high birthweight and asthma. However, several studies, including the PIAMA cohort,²⁷ have also reported an association between

TABLE 1 General characteristics of total PIAMA study population, the population that was excluded from the current analysis, and the study population for analysis (with complete anthropometric data and complete data on atopic sensitization at 8 y of age)

	All PIAMA subjects N=3963	Incomplete data (excluded) N=2355	Population with complete data ^a (included) N=1608	P-value (included vs excluded)
Sex (% females)	1909 (48.2)	1127 (47.9)	782 (48.6)	.631
Maternal education (low level) %	894 (23.5)	565 (25.6)	329 (20.5)	.000
Birth weight, mean±SD	3507.2±546.1	3484.8±568.1	3539.3±511.4	.002
Gestational age, mean±SD	39.8±1.7	39.8±1.7	39.9±1.5	.014
Maternal smoking (pre-natal) %	700 (17.8)	460 (19.8)	240 (15.0)	.000
Smoking exposure (post-natal, 1st year) %	1059 (27.8)	662 (29.9)	397 (24.7)	.000
Born in hospital %	2189 (55.2)	1352 (58.6)	837 (52.4)	.000
Caesarean section %	332 (8.4)	204 (8.9)	128 (8.0)	.353
Breastfeeding >16 wks	1266 (31.9)	664 (28.9)	602 (37.6)	.000
Being LGA	455 (11.8)	261 (11.6)	194 (12.1)	.652
Overweight at 8 y	NA	NA	214 (13.3)	NA
Atopy at 8 y %	NA	NA	653 (40.6)	NA
Maternal allergy %	1237 (31.2)	637 (26.0)	600 (37.3)	.000
Asthma at 8 y %	240 (6.1)	107 (6.3)	133 (8.3)	.031
Asthma at 8 y in atopics %	NA	NA	99 (15.2)	NA
Asthma at 8 y in non-atopics %	NA	NA	34 (3.6)	NA

LGA, large for gestational age; NA, not available; NS, not significant.

^aGestational age, birthweight, anthropometry, atopy and asthma at age 8 y.

TABLE 2 Cross table of presence of asthma at 8 y for combinations of large for gestational age (LGA) and overweight (OW) and stratification by atopy

OW	LGA	All children (N=1608)		Atopic children (N=653)		Non-atopic children (N=955)	
		Asthma n/N (%)	Crude OR	Asthma N (%)	Crude OR	Asthma n/N (%)	Crude OR
–	–	98/1236 (7.9)	1.0	76/506 (15.0)	1.0	22/730 (3.0)	1.0
+	–	10/158 (6.3)	0.8 (0.4-1.5)	9/61 (14.8)	1.0 (0.5-1.1)	1/97 (1.0)	0.3 (0.1-2.5)
–	+	18/178 (10.1)	1.3 (0.7-2.2)	11/74 (14.9)	1.0 (0.5-2.0)	7/104 (6.7)	2.3 (1.0-5.6)
+	+	7/36 (19.4)	2.8 (1.6-6.6)	3/12 (25.0)	1.9 (0.5-7.1)	4/24 (16.7)	6.4 (2.0-20)
Total		133/1608 (8.3)		99/653 (15.2)		34/955 (3.6)	

TABLE 3 Association between being born LGA and asthma at age 8 years in atopic and non-atopic children, and interaction of being overweight at 8 years and being born LGA on asthma at age of 8 in atopic and non-atopic children

	LGA	All children (N=1608)		Atopic children (N=653)		Non-atopic children (N=955)	
		Adj OR	95% CI	Adj OR	95% CI	Adj OR	95% CI
	–	1.0 (ref)		1.0 (ref)		1.0 (ref)	
	+	1.05	0.61-1.81	0.99	0.48-2.08	1.18	0.48-2.90
OW	LGA						
–	–	1.0 (ref)		1.0 (ref)		1.0 (ref)	
+	–	0.78	0.40-1.54	0.99	0.46-2.11	0.34	0.45-2.57
–	+	1.27	0.74-2.19	0.96	0.47-1.93	2.32	0.94-5.73
+	+	2.67	1.11-6.44	0.67	0.43-6.47	7.04	2.02-24.4

Adjusted for sex, maternal smoking (smoking during at least the first 4 weeks of pregnancy), breastfeeding (>16 weeks), born in hospital (yes/no), born by caesarean section (yes/no), maternal educational level and maternal allergy. LGA, large for gestational age; OW, overweight. If the difference is statistically significant at the 95% confidence levels, results are marked in bold.

birthweight and respiratory symptoms, which has been mainly observed among low birthweight children. Therefore, associations between birthweight and asthma may be missed if only linear associations are investigated without addressing the possibility of a U-shaped association. Moreover, as birthweight is highly dependent on gestational age, LGA may be a better marker of increased growth velocity in fetal life than high birthweight or increased ponderal index.²⁶ A recent meta-analysis did not find an association between high birthweight and asthma.²⁸ However, this meta-analysis did not include atopy or current weight status in the analysis.

Our findings suggest that having been born LGA and being overweight at age of 8 significantly increases the risk of asthma in non-atopic children. In similar analyses, we did observe a significantly increased odds of asthma in girls, but not in boys that were both born LGA and overweight. Although there was a difference between girls and boys, the difference was not as big as that observed difference between atopic and non-atopic children. The association between overweight and asthma could be related to respiratory physiology because of the disadvantage of chest muscle function associated with overweight.²⁹ Alternatively, LGA and overweight may influence the development of the immune system, increasing the risk of non-allergic airway inflammation.²⁹ Also, fetal life may be important in modulating genes—possibly through epigenetic mechanisms—that are associated both with overweight and asthma.³ The possibility of shared genetic variants that increase the risk for LGA, overweight and asthma should also be considered. It has been

suggested that the determinants and underlying causal mechanisms of atopic and non-atopic asthma may be different.¹⁷ Classic atopic asthma has been found to be predominantly associated with allergic inflammation with a relative bias towards a Th2 response.¹⁹ In the MeDALL study, which included 12 European cohorts, 45.6% of the asthmatic children did not have atopy at 8 years of age.¹⁶ Thus, although atopy is associated with asthma, a significant proportion of childhood asthma can occur among non-atopic children. Previous studies have shown that markers of early life adiposity (high birthweight or increased neonatal size) are linked to subsequent childhood overweight/obesity and may be associated with asthma independent of atopy or atopic comorbidities.^{8,9} Our findings, however, suggest that obesity may be involved in increasing the risk of this non-atopic phenotype in particular.

The present study has some limitations. First, although our study population consisted of more than 1600 children, our main findings were based on the interaction between LGA and overweight on asthma at 8 years. Given the stratification of the study population, the numbers of children with asthma in some of the strata were relatively small. Therefore, it is important to evaluate the generalizability of our findings of an interaction between LGA and overweight on asthma in non-atopic children in other independent cohorts. Second, although some misclassification of LGA may have occurred (LGA frequency=12.3%, we used the most recent reference values for the Dutch population). It is, however, unlikely that this misclassification is associated with later development of asthma.²¹ PIAMA has

recently linked the questionnaire data to the national birth registry using birthweight as one of the linkage variables and was able to successfully link >90% of the PIAMA participants, indicating that birthweight was nearly always correctly reported in the parental questionnaires. Third, our findings are based on data that are more than 10 years old. Although there were no major changes in the prevalence of overweight among 8-year-old in the Netherlands between 1997 and 2009³⁰ and no major changes in the prevalence of asthma among 0 to 14-year-old between 2004 and 2010 (<https://www.volksgezondheidszorg.info/onderwerp/astma/cijfers-context/trends#!node-trend-prevalentie-astma-naar-leeftijd>), we cannot rule out changes in overweight status and asthma as the data have been collected. Such changes may have impacted the generalizability of our findings to the present situation, but not the internal validity of our results.

The relatively small sample size of the present study is largely explained by the availability of specific IgE data from the 8-year clinical examination, which was performed in a subgroup only. As the study population is not a random sample of the full cohort and for example highly educated, and allergic parents are over-represented, the generalizability of our findings to the full cohort and to the general population may be limited. However, the results were largely unchanged by adjustment for potential confounders, including maternal atopy and maternal education, and therefore, this over-representation most likely did not affect our results.

In summary, we have shown that non-atopic children born LGA who were also overweight by 8 years have an increased risk of asthma at age 8. If confirmed, these findings suggest that children born LGA may be identified as a high-risk group early in life and may benefit from interventions on overweight prevention at school age.

AUTHOR CONTRIBUTIONS

Leonardo A. Pinto was responsible for writing the research project, data analysis, manuscript writing and submission. Alet Wijga and Henriette Smit contributed and supervised the project definition, data analysis and writing. Josep Maria Anto supervised data analysis and manuscript writing. Stefano Guerra supervised and contributed to data analysis and writing. Dirkje Postma, Gerard H. Koppelman, Johan C. de Jongste, Ulrike Gehring contributed to the conception, continuity of the cohort, collection of data and the manuscript reviewing.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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