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TITLE PAGE

Title:

Rapid early weight gain is associated with wheeze and reduced lung function in childhood.

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Contributions:

The guarantor of this study is CE who is responsible for the integrity of the work as a whole, from conception and design to conduct of the study and acquisition of data, analysis and interpretation of data and writing of the manuscript. AG, CE and CU designed the study. AG, MK and AE were responsible for data acquisition. AG performed the analysis and wrote the manuscript. All authors were involved in interpretation of the data and contributed to the critical review of the report. All authors approved the final version of the article before submission.

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Ethical approval:

The medical ethics committee of the University Medical Centre Utrecht approved the study. Written informed parental consent was obtained from all parents of participating children.

Word count: 3544 words

ABSTRACT

To investigate the association between rapid weight gain in the first 3 months of life and the prevalence of wheeze in the first years of life and lung function at 5 years of age.

Infants participate in an ongoing birth cohort. Information on growth and respiratory symptoms was collected during the first year of life, and on primary care consultations during total follow-up. Forced expiratory volume in 1 second (FEV_1) and maximal mid expiratory flow (FEF_{25-75}) were measured at 5 years of age.

Information on growth and respiratory symptoms was obtained for 1431 infants, and 235 children had already 5 years of follow-up. Every z-score increase in weight gain resulted in an increase in days with wheeze by 37% (Incidence Rate Ratio 1.37, 95%CI 1.27-1.47, p<0.001) and in-wheeze-associated consultations by 16% (1.16, 1.01-1.34, p=0.04). Children with rapid weight gain reported significantly more physicians' diagnosed asthma. FEV_1 and FEF_{25-75} were reduced by 34 ml (–0.034 (–0.056-–0.013, p=0.002)) and 82 ml (–0.082 (–0.140-–0.024, p=0.006)) per every z-score increase in weight gain. These associations were independent of birth weight.

Rapid early weight gain is a risk factor for clinically relevant wheezing illnesses in the first years of life and lower lung function in childhood.

Abstract word count: 208

Key words: consultations, infants, lung function, weight gain, wheezing

INTRODUCTION

Wheezing illnesses are highly prevalent during childhood. Almost half of all children experience wheezing during the first years of life and about 10% experiences asthma beyond the age of 6(1;2). Wheezing illnesses have a major impact on children and their families(3) and account for a large number of primary health care consultations in the first years of life(4). The prevalence of wheezing illnesses in affluent countries has been increasing(5;6) parallel to the prevalence of obesity(7). Although wheezing illnesses seem to be related to obesity, data in children are conflicting(8-10). Rapid weight gain in the first years of life is a risk factor for the development of obesity(11;12), but also for other chronic conditions, such as cardiovascular disease and type 2 diabetes(13). A few studies have suggested that rapid weight gain during infancy is also a risk factor for respiratory morbidity and decreased infant lung function. In children with frequent intermittent wheezing, rapid weight gain between birth and the age of 3 was associated with urgent physician visits and more frequent prednisone courses(14). Accelerated weight gain during infancy was associated with more wheezing at the age of 3(15;16), as well as in early adulthood(17). Additionally, rapid postnatal weight gain was associated with impaired lung function development in infancy(18;19).

Importantly, none of these studies focused on weight gain in the first 3 months of life, while this may be a critical growth period. A recent study showed that rapid weight gain in the first 3 months of life, but not in other quarters of the first year of life, was associated with several determinants of cardiovascular disease measured in early adulthood(13). Although the underlying mechanism responsible for the association between rapid weight gain and cardiovascular disease may differ from that of rapid weight gain and respiratory outcomes, the first 3 months after birth do seem to be a critical growth period. Moreover, previous studies have not investigated prospectively collected data on respiratory symptoms and consultations in infancy as outcomes. Furthermore, to our knowledge no study to date has shown an association between accelerated growth in the first months of life and lung function in childhood. More information on the relationships between rapid early weight gain and wheezing illnesses and lung function in healthy infants is needed to further support evidence-based patient information on feeding and growth of newborns and to reduce the burden for families and the health care system.

In a large prospective birth cohort of healthy infants we study whether rapid growth in the first 3 months of life is associated with the number of days with wheezing symptoms in the first year of life, the number of primary care consultations for wheezing in the following years and lung function in childhood.

METHODS

Study design and study population

Infants participate in the ongoing WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a prospective birth cohort on respiratory illnesses that started December 2001(20). Exclusion criteria are gestational age <36 weeks, major congenital abnormalities and neonatal respiratory disease. Parents of all healthy newborns in Leidsche Rijn, with a general practitioner in one of the collaborating health centres, were asked to participate. At the age of 3-8 weeks information on pre- and postnatal risk factors was obtained by questionnaires. At the age of 5 children were invited for lung function assessment. The medical ethics committee of the University Medical Centre Utrecht approved the study. Written informed parental consent was obtained.

Definitions of exposures and outcomes

Birth weight and length were measured in the hospital or by the midwife in a standardised way, by using a standard electronic scale and an infant stadiometer as used in the Child Health Care Centres. In the Netherlands infants regularly visit Child Health Care Centres for standardised anthropometry. Anthropometrics are recorded in a personal file, which every child owns. Parents were asked to use this file to report the anthropometric measures in monthly questionnaires.

Follow-up information for wheezing during the first year of life was obtained by daily questionnaires filled in by the parents. Parents were carefully instructed by one of the investigators on how to recognise wheezing. Wheezing was defined as a positive answer to the question “Did your child wheeze (whistling sound from the chest) today?” Parents were asked to return these questionnaires monthly and if necessary reminders were sent.

Data on primary care visits during the first years of life was obtained from the general practitioners’ electronic patient files. Physician-diagnosed wheeze is assessed using different categories of wheezing illnesses in primary care, according to the International Classification of Primary Care (ICPC)(21).

At the age of 5 years information about respiratory symptoms during the previous years was assessed by a questionnaire and forced vital capacity (FVC) manoeuvres were obtained using a heated Lilly head pneumotachometer system (Viasys Healthcare, Hochberg, Germany). Measurements were body temperature, pressure, and saturation (BTPS) corrected and performed conform the latest American Thoracic Society (ATS)/European Respiratory Society (ERS) statement for lung function measurements in preschoolers(22). At least two reproducible flow-volume curves were obtained. The largest forced expiratory volume in 1 second (FEV_1) was selected and maximal mid-expiratory flow (FEF_{25-75}) was obtained from the curve with highest sum of FEV_1 and FVC.

In the WHISTLER-project neonatal lung function was also measured. Further details about this measurement and the association with weight gain are given in the online depository.

A positive history of parental allergy was defined as questionnaire-reported allergy either to pollen, house dust mite, pets or food. Active maternal smoking during pregnancy was considered present if the mother smoked at least one cigarette per day during pregnancy. Smoke exposition after birth was defined as the child being exposed to environmental cigarette smoke for at least 2 hours per week. Maternal higher education was defined as higher vocational or university education.

Analysis

In order to assess differences between children with and without data on growth, with and without available medical records and with and without lung function measurement at 5 years of age, chi-square-tests and t-tests were used. Within the entire WHISTLER cohort Z-scores of weight were calculated at birth and at 3 months, indicating the ranks in the respective weight distributions. As not all children were weighed at exactly 3 months, the weight closest to this age was used (minimum age 60 days, maximum age 120 days) and z-scores were adjusted for the exact age in days by using linear regression. Weight gain was calculated as the difference between z-scores of weight at birth and at 3 months of age. Subsequently, rapid weight gain was defined as a change greater than 0.67 z-score, normal weight gain as a change in z-score between -0.67 and 0.67 and slow weight gain as a change of -0.67 z-score or less(14). To assess possible confounding factors, baseline characteristics of groups of children with these three different weight gain patterns were tested using chi-square, ANOVA or Kruskal-Wallis tests, where appropriate.

The number of days with wheezing symptoms between the 4th and 12th month of age was used as a count type outcome, best fitting a negative binomial distribution, due to many children with no days of wheezing symptoms. Negative binomial regression was used, with the number of days with wheezing symptoms between the 4th and 12th month as a dependent variable and weight gain as an independent continuous variable. The number of returned monthly questionnaires was used as an offset variable to indicate exposure time. Poisson regression was used to analyse the association between weight gain and the number of primary care consultations for wheezing illnesses in the groups of infants with at least 12 and 36 months of follow-up and additionally in the whole group. The follow-up duration in months was used as an offset variable. In order to take the dependent nature of the primary care consultations for an individual patient into account, a mixed effects Poisson regression model was used, with a random effect for the patients and fixed effects for weight gain and other variables. Linear regression analysis was used to assess the association between weight gain in the first 3 months and FEV_1 and FEF_{25-75} adjusted for age and length.

For all the analyses, the crude association was first calculated. Secondly, the model was adjusted for gender and gestational age. Thirdly, the model was additionally adjusted for siblings and ethnicity of the mother, because these factors may be associated with weight gain and wheezing symptoms and lung function, and these were not equally distributed according to infants with different weight gain patterns. Although maternal smoking during pregnancy, and the duration of exclusive breastfeeding were not significantly differently distributed in the groups with different weight gain patterns, these variables could be clinically relevant as they may be associated both with weight gain and wheezing symptoms and lung function. Therefore the model was also adjusted for these variables.

To determine whether the association was present in children with low birth weight (z-score<0) as well as high birth weight (z-score≥0), the analyses were repeated after stratification according to birth weight. All the analyses were repeated with length gain as an independent continuous variable. Results are presented as incidence rate ratios (IRR), indicating relative change in outcome rates, and linear regression coefficients, 95%

confidence intervals and p-values. Associations were considered statistically significant if p-values were <0.05. Analyses were run using SPSS (version 15.0, SPSS Inc., 2007, Chicago USA) or the statistical program R (Package 2.12.2, http://www.R-project.org/).

RESULTS

Figure 1 shows an overview of the characteristics of infants that have been included in the ongoing WHISTLER-study. In 89% of the children data on both weight gain and wheezing symptoms were obtained and in 83% data on primary care consultations were available. In 87% of the children who already had five years of follow-up, valid lung function measurements were obtained (mean age: 5.3 years; SD: 0.2 years). No differences were found between infants with and without data on growth, with and without information on consultations and with and without lung function measurement at 5 years of age, in terms of parental allergy, gestational age, gender, siblings, maternal smoking during pregnancy, birth weight, born small for gestational age (SGA), ethnicity of the mother and exclusive breastfeeding in the first quartile (Table 1). Table 2 shows baseline characteristics for different weight gain patterns. Infants with rapid weight gain were more likely to be male, born after a shorter gestation period with a lower birth weight and length, more often SGA and were less frequently born to mothers of western origin and less likely to have siblings.

Early weight gain pattern and wheezing in the first year of life

The mean number of returned questionnaires during the 4^{th} and 12^{th} month was 7.8. In the group with rapid weight gain this was 7.5. 95% of the parents completed the questionnaires in the second quartile, 89% in the third quartile and 84% in the fourth quartile. Between the 4^{th} and 12^{th} month of the first year of life 36% of all infants had wheezing symptoms and 15%

had more than 7 days of wheezing. 21% of the children wheezed in the second quartile, 21% in the third quartile and 19% in the fourth quartile.

With increasing weight gain a higher percentage of the children wheezed (figure 2a) and infants experienced more days with wheezing symptoms (figure 2b) (Kruskal-Wallis test p=0.001). Table 3 shows a 37% higher rate of days with wheezing symptoms per 1 z-score increase in weight gain, after adjustment for gender, gestational age and other potential confounders. Significant associations were found within children with low or high birth weight (IRR 1.29 (95% CI: 1.16-1.43, p<0.001) vs. IRR 1.48 (95% CI: 1.33-1.64, p<0.001)). No significant association was found between length gain and days with wheezing symptoms, after adjustment for confounders (IRR 1.05, 95% CI: 0.96-1.15, p=0.221).

Early weight gain pattern and primary care consultations for wheezing illnesses until the age of 5

Median follow-up time for primary care consultations was 38.2 months (range 1-91); 1217 infants had at least 1 year of follow-up, and 711 infants at least 3 years. 25.2% of all infants had at least one primary care consultation for wheezing illnesses during the first year of life, 39.7 % of all infants during the first 3 years of life, and 47.5% during the first 5 years of life. Table 3 shows that one z-score increase in weight gain was related to a 26% higher rate of primary care consultations for wheezing illnesses in the first year of life, a 23% higher rate in the group of children with 3 years of follow-up, and an 16% higher rate in the total group, accounting for follow-up duration. Stratification according to birth weight did not materially influence the results, and no significant association was found between length gain and primary care consultations for wheezing illnesses (data not shown).

Early weight gain pattern and wheeze and lung function at the age of 5

Of the 5-year old children with rapid weight gain, 32.1% reported wheezing over the last 12 months, which was significantly more often than the children with normal (7.7%) or slow (19.0%) weight gain (Chi-square: p=0.020). Furthermore, they reported significantly more often to have had a physician's diagnosis of asthma (18.2% versus 3.3% and 3.5%, Chi-square: p= 0.001). Mean FEV_1 at the age of 5 was 1.280 l (SD: 0.177 l) and mean FEF_{25-75} was 1.502 l (SD: 0.386 l). Table 4 shows that, after adjustment for confounders, one z-score increase in weight gain was associated with a significant decrease in FEV_1 (minus 34 ml (–2.7 %)) and a significant decrease in FEF_{25-75} (minus 82 ml (–5.4 %)). After stratification according to birth weight, the same associations were found in both groups (Table 4). No significant association was found between length gain and lung function (data not shown).

Results on the association between weight gain and neonatal lung function measurement are given in the online depository.

DISCUSSION

This study shows that rapid weight gain in the first 3 months after birth is associated with clinically relevant wheezing illnesses in the first years of life and a decreased lung function at 5 years of age, and that this association is independent of birth weight.

In our cohort, wheezing complaints were only prospectively documented during the first year of life. Primary care consultations were obtained for the total follow-up period. The association between rapid weight gain and primary care consultations seemed to be somewhat stronger in the first year than in the following years, suggesting that the effect diminishes with increasing age. One explanation could be that at an older age other factors play an increasingly important role on wheezing symptoms and consultations. Follow-up of our cohort will determine if the effect of rapid weight gain on respiratory symptoms persists, or disappears during childhood, relative to other causes. Nevertheless, in the 5-year old subgroup that experienced rapid weight gain in the first 3months, a significantly higher percentage reported wheezing over the last 12 months and a physicians' diagnosis of asthma.

Only a few studies have investigated the relationship between rapid growth and wheezing symptoms(14-17). Although these studies investigated different domains and different periods of weight gain and outcome, they showed similar results. Our results are also in accordance with studies showing decreased lung function after rapid postnatal growth(18;19). To our knowledge only one study has analyzed the association between rapid weight gain and childhood spirometry but was unable to show a significant association(18).

Several mechanisms may be responsible for our findings. According to Barker's hypothesis(23) chronic conditions later in life are due to an unfavourable foetal environment, with retarded growth in utero and compensatory growth after birth. Later studies showed that especially rapid compensatory growth seems to be a risk factor for future outcomes(24;25). In our study the children in the group with rapid weight gain had a lower birth weight and there was a higher prevalence of infants born small for gestational age (SGA). However, we found that the association was present in both subgroups after stratification according to birth weight. Independent of baseline weight, rapid weight gain has a negative effect on outcome. The 'mismatch hypothesis' proposes that especially the difference between the foetal environment and the environment after birth could result in diseases later in life(26). Another possible explanation is chronic inflammation. Obesity can be seen as a state of chronic, low-grade, systemic inflammation. Contrary to rapid length gain, rapid weight gain was specifically associated with wheezing symptoms. Although not all children with rapid weight gain were obese, there was acquisition of adipose tissue. Adipokines, chemokines and other serum factors from adipose tissue could lead to inflammation at other sites(27), such as the airways, leading to consequent wheezing complaints. Since small airways and viral infections play an important role in wheezing in the first years of life(1), our findings may also be explained by disproportional growth. A rapid increase of weight may cause lung development to lag behind somatic growth. The association between rapid weight gain and reduced neonatal lung function shows that the effect is already present in early infancy. As neonatal lung function is associated with later wheezing symptoms, one could expect neonatal lung function to be an intermediate in the causal chain. However, adjustment for neonatal lung function did not significantly influence the association.

Although the mechanism is not completely clear, the results of this study may have implications for clinical practice. Although not all wheezing illnesses will develop into asthma, we believe that an improved control of weight gain and the reduction of unnecessary rapid weight gain, could help diminish the burden of wheezing illnesses in children and their families, and the associated burdens to primary health care.

The strength of this study is the large sample size of healthy newborns and the prospective and standardised manner in which data was collected. Data on wheezing symptoms were collected on a daily basis and we were able to adjust for the most important confounders. However, some methodological considerations should be made. Firstly, information on wheezing symptoms was obtained from questionnaires with parent-reported symptoms, which may be misclassified due to confusion about the distinction between wheeze and snoring or cough(28). We minimised this by careful parental instruction and the percentage of children with wheezing complaints was similar to other studies(29;30). More importantly, the possible misclassification is probably non-differential, and therefore unrelated to weight gain pattern. Secondly, not all parents completed all monthly questionnaires during the first year of life of their child, and this was even slightly lower for the group with rapid weight gain compared to the other weight gain groups. In most instances, the last questionnaires were missing. The number of returned questionnaires was used as offset in the analysis. Due to the fact that the prevalence of wheezing symptoms was comparable during different quartiles of the first year of life, the missing questionnaires would probably not have influenced the association. At the time of analysis only a subgroup of the children in our study population had already reached the age of 5. As this subgroup had the same characteristics as the total cohort and was representative of the total cohort, we considered the significant association between weight gain and lung function as a valuable addition to the other results. Thirdly, it was not possible to adjust for respiratory infections because we were not able to differentiate wheezing illnesses, with and without respiratory infections, from the monthly questionnaires and from the primary care consultations. However, in young children wheezing illnesses are frequently associated with respiratory infections. In a previous study we showed that in almost all respiratory episodes in infants one or more respiratory pathogens were detected(31). Fourthly, we calculated z-scores based on our own population, instead of using age-related, gender-specific growth charts. The mean birth weight and weight at 3 months are comparable to the average weights according to (inter)national growth charts(32;33). Moreover, the relevance of our findings pertains to within group relative growth patterns, and when using international growth charts to calculate z-scores, the same results were found. Weight gain was initially not adjusted for gender and gestational age, and therefore boys are overrepresented in the rapid weight gain group. Gender is associated with weight gain and with wheezing illnesses and this variable was therefore taken into account as a potential confounder in the multivariate regression, instead of only adjusting weight gain for gender. Fifthly, the percentage of mothers that smoked during pregnancy in our cohort is quite low, compared to other cohort studies. However, the rates of maternal smoking throughout pregnancy decreased significantly in the Netherlands during the last decades to 7.6% in 2007(34). As smoking during pregnancy is associated with reduced birth weight and increased wheezing symptoms, it could be a confounder. After adjustment for maternal smoking during pregnancy, the results did not change. However, other results might be found in populations with a higher prevalence of maternal smoking during pregnancy. Lastly, measuring lung function at the age of 5 years is difficult. However the measurements were performed by experienced lung function analysts according to the latest ATS/ERS statement and were successful in a majority of the children.

In conclusion, this study showed that rapid early postnatal weight gain is associated with an increased incidence of parental-reported and physician-diagnosed wheezing illnesses in the first years of life and reduced lung function at 5 years of age.

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REFERENCES

Reference List

(1) Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995 January 19;332(3):133-8.

(2) Matricardi PM, Illi S, Gruber C, Keil T, Nickel R, Wahn U, Lau S. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. Eur Respir J 2008 September;32(3):585-92.

(3) Mohangoo AD, Essink-Bot ML, Juniper EF, Moll HA, de Koning HJ, Raat H. Health-related quality of life in preschool children with wheezing and dyspnea: preliminary results from a random general population sample. Qual Life Res 2005 October;14(8):1931-6.

(4) Stevens CA, Turner D, Kuehni CE, Couriel JM, Silverman M. The economic impact of preschool asthma and wheeze. Eur Respir J 2003 June;21(6):1000-6.

(5) Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? Lancet 2001 June 9;357(9271):1821-5.

(6) Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, Williams H. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006 August 26;368(9537):733-43.

(7) Van CJ, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. JAMA 2010 February 17;303(7):623-30.

(8) Schachter LM, Peat JK, Salome CM. Asthma and atopy in overweight children. Thorax 2003 December;58(12):1031-5.

(9) Scholtens S, Wijga AH, Seidell JC, Brunekreef B, de Jongste JC, Gehring U, Postma DS, Kerkhof M, Smit HA. Overweight and changes in weight status during childhood in relation to asthma symptoms at 8 years of age. J Allergy Clin Immunol 2009 June;123(6):1312-8.

(10) Chinn S, Downs SH, Anto JM, Gerbase MW, Leynaert B, de MR, Janson C, Jarvis D, Kunzli N, Sunyer J, Svanes C, Zemp E, ckermann-Liebrich U, Burney P. Incidence of asthma and net change in symptoms in relation to changes in obesity. Eur Respir J 2006 October;28(4):763-71.

(11) Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ 2005 October 22;331(7522):929.

(12) Hui LL, Schooling CM, Leung SS, Mak KH, Ho LM, Lam TH, Leung GM. Birth weight, infant growth, and childhood body mass index: Hong Kong's children of 1997 birth cohort. Arch Pediatr Adolesc Med 2008 March;162(3):212-8.

(13) Leunissen RW, Kerkhof GF, Stijnen T, Hokken-Koelega A. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. JAMA 2009 June 3;301(21):2234-42.

(14) Paul IM, Camera L, Zeiger RS, Guilbert TW, Bacharier LB, Taussig LM, Morgan WJ, Covar RA, Krawiec M, Bloomberg GR, Mauger DT. Relationship between infant weight gain and later asthma. Pediatr Allergy Immunol 2009 August 27.

(15) Taveras EM, Rifas-Shiman SL, Camargo CA, Jr., Gold DR, Litonjua AA, Oken E, Weiss ST, Gillman MW. Higher adiposity in infancy associated with recurrent wheeze in a prospective cohort of children. J Allergy Clin Immunol 2008 May;121(5):1161-6.

(16) Pike KC, Crozier SR, Lucas JS, Inskip HM, Robinson S, Roberts G, Godfrey KM. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. Thorax 2010 December;65(12):1099-106.

(17) Rona RJ, Smeeton NC, Bustos P, Amigo H, Diaz PV. The early origins hypothesis with an emphasis on growth rate in the first year of life and asthma: a prospective study in Chile. Thorax 2005 July;60(7):549-54.

(18) Turner S, Zhang G, Young S, Cox M, Goldblatt J, Landau L, Le SP. Associations between postnatal weight gain, change in postnatal pulmonary function, formula feeding and early asthma. Thorax 2008 March;63(3):234-9.

(19) Lucas JS, Inskip HM, Godfrey KM, Foreman CT, Warner JO, Gregson RK, Clough JB. Small size at birth and greater postnatal weight gain: relationships to diminished infant lung function. Am J Respir Crit Care Med 2004 September 1;170(5):534-40.

(20) Katier N, Uiterwaal CS, De Jong BM, Kimpen JL, Verheij TJ, Grobbee DE, Brunekreef B, Numans ME, van der Ent CK. The Wheezing Illnesses Study Leidsche Rijn (WHISTLER): rationale and design. Eur J Epidemiol 2004;19(9):895-903.

(21) Verbeke M, Schrans D, Deroose S, De MJ. The International Classification of Primary Care (ICPC-2): an essential tool in the EPR of the GP. Stud Health Technol Inform 2006;124:809-14.

(22) Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, Bisgaard H, Davis GM, Ducharme FM, Eigen H, Gappa M, Gaultier C, Gustafsson PM, Hall GL, Hantos Z, Healy MJ, Jones MH, Klug B, Lodrup Carlsen KC, McKenzie SA, Marchal F, Mayer OH, Merkus PJ, Morris MG, Oostveen E et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med 2007 June 15;175(12):1304-45.

(23) Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. Lancet 1993 April 10;341(8850):938-41.

(24) Stettler N, Zemel BS, Kumanyika S, Stallings VA. Infant weight gain and childhood overweight status in a multicenter, cohort study. Pediatrics 2002 February;109(2):194-9.

(25) Singhal A, Cole TJ, Fewtrell M, Kennedy K, Stephenson T, Elias-Jones A, Lucas A. Promotion of faster weight gain in infants born small for gestational age: is there an adverse effect on later blood pressure? Circulation 2007 January 16;115(2):213-20.

(26) Pike KC, Hanson MA, Godfrey KM. Developmental mismatch: consequences for later cardiorespiratory health. BJOG 2008 January;115(2):149-57.

(27) Shore SA. Obesity and asthma: possible mechanisms. J Allergy Clin Immunol 2008 May;121(5):1087-93.

(28) Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? Arch Dis Child 2000 April;82(4):327-32.

(29) Wright RJ, Cohen S, Carey V, Weiss ST, Gold DR. Parental stress as a predictor of wheezing in infancy: a prospective birth-cohort study. Am J Respir Crit Care Med 2002 February 1;165(3):358-65.

(30) Visser CA, Garcia-Marcos L, Eggink J, Brand PL. Prevalence and risk factors of wheeze in Dutch infants in their first year of life. Pediatr Pulmonol 2010 February;45(2):149-56.

(31) van der Zalm MM, Uiterwaal CS, Wilbrink B, de Jong BM, Verheij TJ, Kimpen JL, van der Ent CK. Respiratory pathogens in respiratory tract illnesses during the first year of life: a birth cohort study. Pediatr Infect Dis J 2009 June;28(6):472-6.

(32) WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl 2006 April;450:76-85.

(33) W.J.M.Gerver RdB. Paediatric Morphometrics. A Reference Manual (2nd extended edition). Universitaire Pers Maastricht; 2001.

(34) Lanting CI, Buitendijk SE, Crone MR, Segaar D, Bennebroek GJ, van Wouwe JP. Clustering of socioeconomic, behavioural, and neonatal risk factors for infant health in pregnant smokers. PLoS One 2009;4(12):e8363.

FIGURE LEGENDS

Figure 1. Overview of the study population.

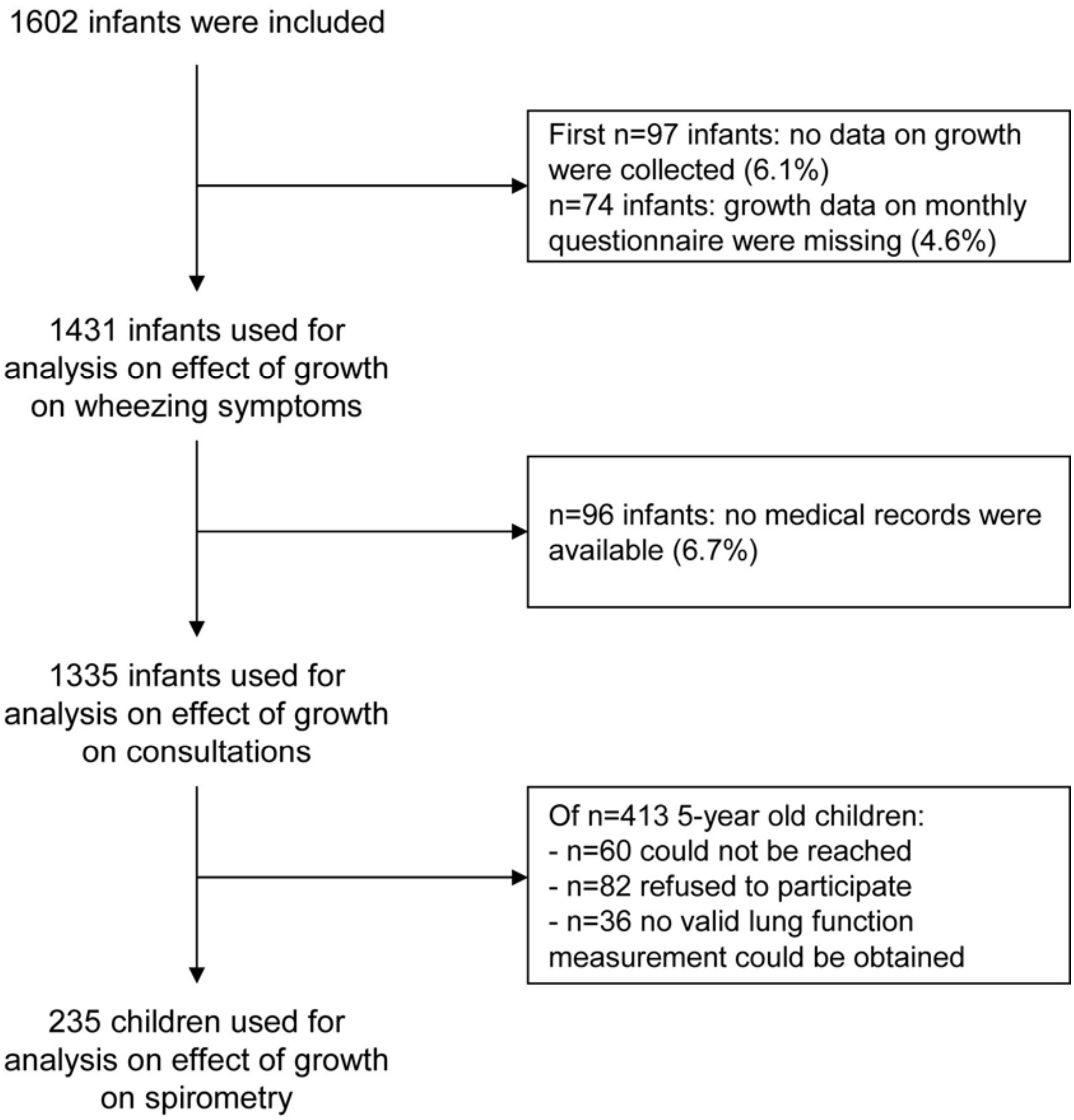


Figure 2. Percentage of children with wheezing complaints (2a) and the amount of wheezing complaints (2b) in the 4th to 12th month of life per weight gain category. Categories of weight gain: Δ weight z-scores between birth and 3 months. **Slow** weight gain: Δ z-score < -0.67, **Normal** weight gain: Δ z-score ≥ -0.67 and < 0.67, **Rapid** weight gain: Δ z-score ≥ 0.67. 2a Chi-square test p<0.001.

Figure 2a

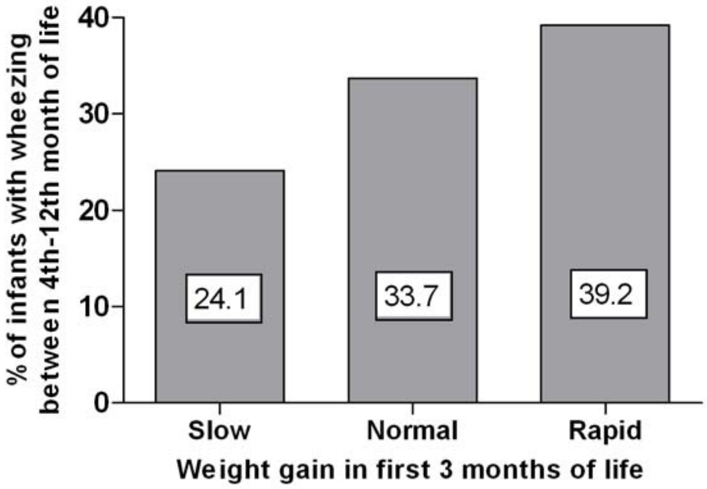
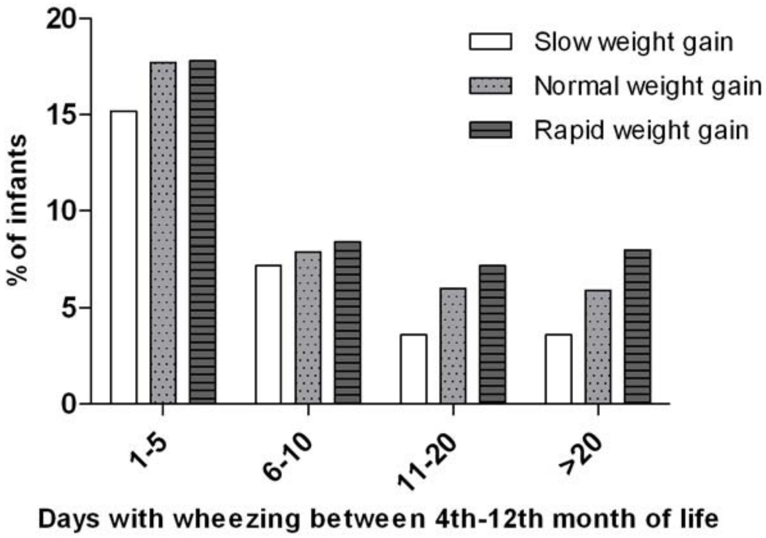


Figure 2b



TABLES

Table 1. General characteristics of the different subgroups that were studied.

	Total group	Group with complete growth data and daily symptoms	Group with complete growth data and medical records	Group with lung function at age 5 years
	N = 1602	**N = 1431**	**N = 1335**	**N = 235**
Sex (% boys)	49.3	48.6	49.5	45.3
Birth Weight (mean, grams)	3525	3525	3529	3503
Gestational age (mean days)	278.6	278.6	278.7	279.2
Small for Gestational age (weight for gestational age < 10^{th} percentile) (%)	9.7	9.6	9.6	11.1
Maternal allergy (allergy to pollen, house dust mite, food, or pets) (%)	37.6	38.6	39.4	37.4
Paternal allergy (allergy to pollen, house dust mite, food, or pets) (%)	37.5	37.2	38.1	38
Exclusive breastfeeding (median, wks)	6.4	6.9	6.3	6.1
Siblings (% with at least one)	51.8	52.5	50.7	49.8
Maternal smoking during pregnancy (%)	5.9	5.6	5.7	6.9
Ethnicity mother (% Western)	90.1	90.7	89.6	90.5

No significant differences between the total group and different subgroups were found (data not shown).

Table 2. Baseline characteristics of total study population by growth pattern.

	Total group N = 1431	Slow weight gain N = 338	Normal weight gain N = 770	Rapid weight gain N = 323	Statistics
Sex (% boys)	48.6	31.7	47.4	69.3	**<0.001[a]**
Birth Weight (mean, in grams)	3525	3859	3500	3237	**<0.001[b]**
Birth Length (mean, in cm)	50.9	51.9	50.9	50.0	**<0.001[b]**
Weight day 90 (mean, in grams)	6069	5703	6042	6516	**<0.001[b]**
Length day 90 (mean, in cm)	61.1	61.1	61.0	61.4	0.119[b]
Gestational age (mean days)	278.6	282.1	278.8	274.5	**<0.001[b]**
Small for Gestational age (weight for gestational age < 10th percentile) (%)	9.6	3.0	7.9	20.7	**<0.001[a]**
Maternal asthma in last 12 months (%)	9.2	7.6	10.0	9.0	0.493[a]
Maternal allergy (allergy to pollen, house dust mite, food, or pets) (%)	38.6	35.0	39.2	41.0	0.313[a]
Paternal asthma in last 12 months (%)	6.4	5.8	6.1	7.7	0.632[a]
Paternal allergy (allergy to pollen, house dust mite, food, or pets) (%)	37.2	37.4	36.3	39.5	0.696[a]
Exclusive breastfeeding (median, wks)	6.9	8.9	7.1	5.9	0.313[c]
Exclusive breastfeeding first 3 months (%)	42.4	46.2	42.0	39.2	0.194[a]
Breastfeeding (with/without formula milk feeding) first 3 months (%)	62.9	66.3	63.5	58.0	0.085[a]
Siblings (% with at least one)	52.5	59.2	50.3	50.6	**0.019[a]**
Pet ownership during pregnancy (%)	40.4	38.5	40.4	42.4	0.585[a]
Pet ownership after birth (%)	39.6	36.9	39.5	42.6	0.337[a]
Maternal smoking during pregnancy (%)	5.6	4.7	5.6	6.5	0.613[a]
Smoke exposition after birth (%)	12.3	12.1	13.2	10.9	0.798[a]
Maternal higher education (%)	66.5	69.3	65.6	65.8	0.527[a]
Birth season (%)					0.792[a]
Winter	22.8	23.1	23.0	22.0	
Spring	25.4	24.3	24.9	27.6	
Summer	26.8	29.0	25.7	27.2	
Autumn	25.0	23.7	26.4	23.2	
Ethnicity mother (% Western)	90.7	93.3	90.9	87.2	**0.048[a]**
Ethnicity father (% Western)	91.6	94.5	90.6	90.6	0.124[a]

Categories of weight gain: Δ weight z-scores between birth and 3 months. **Slow** weight gain: Δ z-score < -0.67, **Normal** weight gain: Δ z-score ≥ -0.67 and < 0.67, **Rapid** weight gain: Δ z-score ≥ 0.67. a= Chi-square test, b= Anova-test, c= Kruskal-Wallis test.

Table 3. Association between weight gain in the first 3 months of life and days with wheezing symptoms or wheezing-associated primary care consultations.

Risk Factor	*Crude* IRR (95% CI)	P-value	*Adjusted* IRR (95% CI)	P-value
	Days with wheezing symptoms ~~in~~ <u>during </u>month<u>s</u> 4-12 (number of monthly questionnaires is offset) (n=1431)			
Weight gain† (per 1 z-score increase)	1.36 (1.27-1.45)	**<0.001**	1.35 (1.26-1.45)*	**<0.001**
			1.37 (1.27-1.47)**	**<0.001**
	Primary care visits for wheezing illnesses in first year of life (n=1217)			
Weight gain† (per 1 z-score increase)	1.33 (1.12-1.16)	**=0.002**	1.26 (1.03-1.53)*	**=0.02**
			1.26 (1.03-1.53)**	**=0.02**
	Primary care visits for wheezing illnesses in first 3 years of life (n=711)			
Weight gain† (per 1 z-score increase)	1.29 (1.09-1.54)	**=0.003**	1.22 (1.01-1.47)*	**=0.04**
			1.23 (1.02-1.48)**	**=0.03**
	Primary care visits for wheezing illnesses during total follow-up (follow-up is offset) (n=1335)			
Weight gain† (per 1 z-score increase)	1.26 (1.11-1.45)	**=0.001**	1.17 (1.01-1.35)*	**=0.03**
			1.16 (1.01-1.34)**	**=0.04**

IRR: incidence rate ratio. † Differences between z-score for weight at age 3 months (adjusted for the exact age in days) and at birth. * adjusted for sex, and gestational age. ** Also adjusted for other potential confounders (maternal smoking during pregnancy, duration of exclusive breastfeeding, siblings, and the ethnicity of the mother).

Table 4. Association between weight gain in the first 3 months of life and lung function (FEV_1 and FEF_{25-75}) at 5 years of age.

Risk Factor		*Crude* Regression coefficient	P-value	*Adjusted* Regression coefficient	P-value
		FEV_1 (l) ‡ (n=235)			
Weight gain† (per 1 z-score increase)	Total group	–0.025 (–0.044 - –0.005)	**0.014**	–0.035* (–0.056 - –0.013)	**0.002**
				–0.034** (–0.056 - –0.013)	**0.002**
	Birth weight < 0 z-score			–0.024** (–0.060 - 0.013)	0.2
	Birth weight > 0 z-score			–0.043** (–0.075- –0.011)	**0.011**
		FEF_{25-75} (l/s) ‡ (n=235)			
Weight gain† (per 1 z-score increase)	Total group	–0.059 (–0.111 - – 0.008)	**0.024**	–0.079* (–0.136 - –0.023)	**0.006**
				–0.082** (–0.140 - –0.024)	**0.006**
	Birth weight < 0 z-score			–0.062** (–0.160 - 0.037)	0.216
	Birth weight > 0 z-score			–0.085** (–0.177- 0.008)	0.073

Beta = linear regression coefficient. † Differences between z-score for weight at 3 months of age (adjusted for the exact age in days) and at birth. ‡ FEV_1 and FEF_{25-75} adjusted for age, and length at measurement. * Adjusted for sex, and gestational age; **Also adjusted for other potential confounders (maternal smoking during pregnancy, duration of exclusive breastfeeding, siblings, and the ethnicity of the mother).