



Body mass index and the incidence of asthma in children

Irene Brüske^a, Claudia Flexeder^{a,b}, and Joachim Heinrich^{a,b,c}

Purpose of review

When evaluating the causal link between obesity and the development of asthma in children, prospective cohort studies are essential. The results of the most recently published birth cohort studies from Sweden, Germany, Brazil, Belarus, and California, USA, as well as from a joint analysis of eight European birth cohorts of the Global Allergy and Asthma European Network are evaluated. Moreover, the results of two meta-analyses are presented.

Recent findings

Most recent prospective cohort studies found a dose–response association between overweight or obesity and asthma. The evidence of effect modification by sex, ethnicity, and age was inconsistent. Both meta-analyses also showed that overweight children were at an increased risk of incident asthma compared with nonoverweight children and that the relationship was further elevated for obesity.

Summary

Prospective cohort studies and two recently published meta-analyses found an association between overweight (and especially obesity) and asthma in the appropriate temporal sequence and in a dose–response manner. Children with a pronounced weight gain slope in early life were particularly at risk for asthma within the first 6 years of life. The gain in BMI over time during infancy may be an even more important predictor for asthma in childhood than excess weight at any specific age.

Keywords

asthma incidence, birth cohorts, obesity, overweight

INTRODUCTION

Obesity and asthma are two very important pediatric health problems in many parts of the world. The simultaneous increase in the prevalence of both conditions over the last 2 decades has raised the concern that the two may be causally related. In fact, obesity is described in the literature as one of the risk factors for asthma development, together with sex, genetic predisposition, and environment [Global Initiative for Asthma (GINA). Bethesda: NHLBI/WHO; 2010. Available at www.ginasthma.com]. Epidemiological studies on obesity and asthma are numerous, but longitudinal cohort studies in children are relatively sparse. Cross-sectional studies are easier to conduct. However, if BMI and asthma are assessed at the same timepoint, the temporal sequence of events is unknown and reverse causation cannot be excluded. When evaluating the causal link between obesity and the development of asthma, prospective cohort studies are therefore essential.

In the following section, the results of the most recently (2012–2013) published prospective birth cohort studies from Sweden [1], Germany [2], Brazil [3], Belarus [4], and California [5], as well as from a joint analysis of eight European birth cohorts participating in the Global Allergy and Asthma European Network (GA²LEN) [6[■]], will be introduced. Readers should be aware that the definitions of obesity and asthma varied across studies, rendering

^aInstitute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, ^bMember of the Network of Competency of Adiposity and ^cGerman Center for Lung Research, Giessen, Germany

Correspondence to Dr Joachim Heinrich, Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany. Tel: +49 89 3187 3213; fax: +49 89 3187 3380; e-mail: brueske@helmholtz-muenchen.de

Curr Opin Allergy Clin Immunol 2014, 14:155–160

DOI:10.1097/ACI.000000000000035

KEY POINTS

- As BMI and asthma are assessed at the same timepoint in cross-sectional studies, whether overweight or obesity affects asthma (or vice versa) cannot be determined. Prospective cohort studies are needed to evaluate this causal link.
- Prospective cohort studies included in the two recently published meta-analyses found an association between overweight (and especially obesity) and asthma in the requisite time sequence and in a dose–response manner.
- Rapid weight gain in early life might be an important risk factor for the development of asthma during childhood and adolescence.

the comparison of results difficult at times. Percentiles of BMI [1], age-specific and sex-specific BMI standard deviation scores (BMI z-scores) [3,6²²], and growth trajectories in infancy, such as peak height velocity (PHV) and peak weight velocity (PWV) [2], were used to define obesity. Asthma was defined in some studies using the prevalence of parent-reported asthma or common asthma symptoms (wheezing), whereas in others reported physician-diagnosed incident asthma was available. An overview of the study parameters investigated and the main results is presented in Table 1 [1–5,6²²–8²³].

REVIEW OF THE RECENT PROSPECTIVE COHORT STUDIES

A birth cohort of newborn infants (BAMSE – Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology) [1] was followed for 8 years, and aimed to examine the associations between high BMI and changes in BMI status during the first 7 years of life and asthma at the age of 8 years. Repeated parental questionnaires provided information on environmental exposures and health outcomes. Information on height and weight during childhood was retrieved from preschool and school healthcare records. The analyses included 2075 children with available information on weight, height, and asthma at the age of 8 years. A high BMI (≥ 85 th percentile) at age 1, 4, and 7 years was associated with an increased risk of asthma at the age of 8 years. However, no significant association was observed among children with high BMI at 12 and 18 months or at 4 years of age, if the children developed a normal BMI by age 7 years. The risk was increased among children with high BMI at age 7 years, regardless of their earlier weight. The study indicated that a high BMI during the first 4 years of

life did not increase the risk of asthma at school age among children who had developed a normal weight by age 7 years.

In contrast, in the GINIplus (The German Infant Nutritional Intervention plus Genetics) and LISA-plus (Influence of Lifestyle and Behaviour on the Development of the Immune System and Allergic diseases plus Air Pollution and Genetics) birth cohorts [2], it was shown that rapid weight gain during infancy was positively associated with physician-diagnosed asthma, and that this association was independent of the current BMI in school-aged children. This study did not consider BMI or obesity, but rather examined the velocity of height and weight gain during infancy. Using data from 9086 German children, associations between peak height and weight velocities during the first 2 years of life and the onset of asthma and wheeze up to 10 years of age were examined. Information on asthma was requested annually from 1 to 6 and at 10 years, and information on wheeze at 1, 2, 4, 6, and 10 years. Peak height and weight velocities were calculated using height and weight measurements obtained between birth and 2 years of age. One interquartile range increase in PWV significantly increased the risk of asthma [adjusted hazard ratio: 1.22; confidence interval (CI): 1.02–1.47]. This increased risk was independent from birth weight and BMI at the age of 10 years. The relationship between PHV and asthma onset was not significant (adjusted hazard ratio: 1.08; CI: 0.88–1.31). Wheeze was not significantly associated with PHV or PWV (adjusted odds ratio: 1.07; CI: 0.64–1.77 and 1.11; CI: 0.68–1.79, respectively).

The Pelotas (Brazil) Birth Cohort Study [3] included all births that occurred in 1993 in the Pelotas city of approximately 340 000 inhabitants in the southern region of Brazil. Of the 5249 members included in the original cohort, 4201 individuals could be located (148 deaths were excluded), which corresponded to a follow-up rate of 85.7% at 15 years of age. The study aimed to investigate the effect of obesity at the start of adolescence on the prevalence, incidence, and maintenance of chest wheezing among individuals aged 11 and 15 years. The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was used to define wheezing. At the age of 11 years, approximately one-third of the adolescents in the cohort were overweight or obese. At the next follow-up, less than 3% of the adolescents had become obese, whereas just over 6% remained obese. Almost one-quarter of the adolescents remained in the upper tertile of the skinfold sum. The prevalences of chest wheezing at 11 and 15 years of age were 13.5% (95% CI: 12.5–14.5%) and 12.1% (95% CI: 11.1–13.1%), respectively.

Table 1. Summary results of the studies reviewed

Study	Weight measure	Follow-up	Study outcome	Observed effect (95% CI)	Adjusted for
BAMSE [1]	High BMI (≥ 85 th percentile)	Birth cohort; follow-up 8 years	Parental questionnaire: asthma was defined as at least 4 episodes of wheezing in the previous 12 months	OR for high vs. normal BMI at 1, 1.5, 4, and 7 years: OR for change in BMI between 4 and 7 years vs. persistent normal (early high: adj. OR: 1.25 (95% CI: 0.58–2.67); late high: 2.09 (1.09–3.98); persistent high: 2.49 (1.38–4.49)	Parental history of allergic disease, sex, breastfeeding duration, birth weight, maternal age, and smoking
GINIplus/ LISAplus [2]	PHV and PWV up to age 2	Birth cohort; follow-up 10 years	Parental questionnaire: physician-diagnosed asthma and wheeze in the last 6 or 12 months, requested annually from 1 to 6 years and at 10 years	Association between physician-diagnosed asthma and PWV (adj. HR: 1.22; <i>P</i> -value: 0.031) but not PHV (adj. HR: 1.08; <i>P</i> -value: 0.466)	Sex, parental education, parental atopy, breastfeeding, number of siblings, maternal smoking during pregnancy, study center, birth weight, and BMI at 10 years of age
Pelotas [3]	Normal: BMI z-score $\leq +1$ SD; overweight: BMI z-score $\leq +2$ SDs; obese: BMI z-score ≥ 2 SDs	Birth cohort; follow-up for 15 years	Parental questionnaire (ISAAC): 'Since <MONTH> of last year has <NAME> had chest wheezing'. Adolescent questionnaire: 'Since <MONTH> of last year have you had chest wheezing?'	Association between weight status and incident wheezing from 11 to 15 years: overweight vs. normal OR 1.07 (0.76–1.51); obese vs. normal OR 1.11 (0.72–1.71)	Sex, skin color, maternal age at delivery, gestational age, hospitalization in infancy, maternal smoking during pregnancy, parents smoking when the child was 11 and 15 years old, and smoking by the adolescent
PROBIT [4]	At least two measures of length/height and weight between birth and 60 months, weight and height at 6.5 years	Birth cohort; follow-up 6.5 years	Parental questionnaire (ISAAC): wheeze ever, wheeze in the last 12 months, allergic rhinitis ever, allergic rhinitis in the last 12 months, eczema ever and asthma ever	Associations between early infancy to mid-childhood weight gain rate (sex-adjusted z-score) and ever asthma: odds of outcome per z-score increase in birth weight; odds of outcome per z-score change in weight gain	Sex, treatment arm, exclusive breastfeeding at 3 months, parents' height and weight, mother's age, family history of atopy, parental education, and preceding weight and length/height

(Continued)

Table 1 (Continued)

Study	Weight measure	Follow-up	Study outcome	Observed effect (95% CI)	Adjusted for
KPSC [5]	'Normal weight' (>5th and <85th percentiles), 'overweight' (>85th and <95th percentiles, or BMI >25), 'moderately obese' (>95th percentile or BMI >30), and 'extremely obese' ($\geq 1.2 \times 95\text{th percentile}$ or BMI ≥ 3.5)	Children at least 6 years old at baseline; median follow-up 3 years	Physician diagnosis of asthma and asthma-specific medication in the same year; the presence of 1 or more asthma-related emergency department visits or hospitalizations in the absence of asthma medication ($n = 926$; 2.9%), or three or more asthma-related ambulatory visits in the absence of asthma medication	Adj. OR for overweight, moderately obese, and extremely obese vs. normal weight were 1.16 (95% CI: 1.13–1.20), 1.23 (95% CI: 1.19–1.28), and 1.37 (95% CI: 1.32–1.42)	Age, sex, and payer for insurance
GA ² LEN [6 ^{***}]	Three subpopulations with similar standardized BMI trajectories according to age/sex-specific WHO growth standards	Six birth cohorts; follow-up 6 years	Parental questionnaire of first-reported doctor-diagnosed asthma within 3 time periods: the first 2 years of life, 3–4 years, and 5–6 years	Children with high BMI-SDS gain in the first 2 years of life had a higher risk for incident asthma up to age 6 years compared with children with a less pronounced weight gain slope in early childhood. The hazard ratio was 1.3 (95% CI: 1.1–1.5)	Birth weight, weight-for-length at birth, gestational age, sex, maternal smoking during pregnancy, breast feeding, and family history of asthma or allergies
Meta-analysis	Weight measure	Follow-up	Study outcome	Observed effect (95% CI)	
Chen <i>et al.</i> [7 ^{***}]	'Overweight' (>85th and <95th percentiles); 'Obese' (>95th percentile) for children of the same age and sex	Children 5–18 years old at baseline	Incident asthma	Overweight vs. nonoverweight RR: 1.19 (95% CI: 1.03–1.37); Obese vs. nonobese RR: 2.02 (95% CI: 1.16–3.50); RR among boys: 2.47 (95% CI: 1.57–3.87) and girls: 1.25 (95% CI: 0.51–3.03)	
Egan <i>et al.</i> [8 ^{***}]	'Overweight' (>85th and <95th percentiles) 'obese' (>95th percentile) for children of the same age and sex	Children under the age of 18 years at baseline	New physician diagnosed asthma at least 1 year after height and weight were measured	Overweight vs. nonoverweight RR: 1.35 (95% CI: 1.15, 1.58); Obese vs. nonobese RR: 1.50 (95% CI: 1.22–1.83); RR among boys: 1.40 (95% CI: 1.01–1.93) and girls: 1.53 (95% CI: 1.09–2.14)	

Adj., adjusted; BMI, body mass index defined as weight in kilograms divided by height in meters squared; CI, confidence interval; HR, hazard ratio; OR, odds ratio; PHV, peak height velocity; PWV, peak weight velocity; RR, relative risk; SD, standard deviation; vs., versus.

In the recent Promotion of Breastfeeding Intervention Trial (PROBIT) study [4] of 12 171 term infants from the Republic of Belarus, weights and lengths/heights were measured at 1, 2, 3, 6, 9, and 12 months and at 6.5 years, and extracted from clinical records. Atopic phenotypes were ascertained at 6.5 years using the ISAAC questionnaire. After controlling for confounders and prior weight and length/height gain, all weight gain variables except birth weight were positively associated with ever having wheezed ($P < 0.1$). In contrast, all atopy outcomes, except for ever having asthma, were associated with current weight and height, even after controlling for prior growth.

A population-based study [5] evaluated the electronic health records of patients aged 6–19 years who were enrolled in the Kaiser Permanente Southern California (KPSC) health plan between 2007 and 2011. Although not originally designed as a prospective cohort study, children with prevalent asthma recorded in their electronic health records were excluded, thereby leaving 623 358 asthma-free patients with baseline height and weight measurements available for follow-up. Crude asthma incidence ranged from 16.9 per 1000 person-years among normal-weight youth to 22.3 per 1000 person-years among extremely obese youth. The adjusted risks of asthma for overweight, moderately obese, and extremely obese youth relative to those of normal weight youth were 1.16 (95% CI: 1.13–1.20), 1.23 (95% CI: 1.19–1.28), and 1.37 (95% CI: 1.32–1.42), respectively (P for trend < 0.0001). The relationship between higher body mass and childhood asthma risk was modified by race/ethnicity, sex, and age. Obesity, especially extreme obesity, had a greater impact on asthma risk in young girls and in Asian/Pacific Islander youth than in other groups.

The GA²LEN [6^{***}] supported a very large prospective longitudinal analysis in younger children. This study aimed to investigate whether the course of BMI predicts incident asthma in childhood. Data on asthma and allergies from 12 050 individuals participating in eight European birth cohorts were combined. Asthma was defined as questionnaire-based parent-reported doctor-diagnosed asthma, and was assessed similarly by all included cohorts. The outcome ‘incident asthma’ was defined as first-reported asthma diagnosis within three time periods: the first 2 years of life, 3–4 years, and 5–6 years. BMI and doctor-diagnosed asthma were modeled during the first 6 years of life with latent growth mixture modeling and discrete time hazard models. Subpopulations of children were identified with similar standardized BMI trajectories according to age-specific and sex-specific ‘World Health Organization (WHO) child growth standards’ and

‘WHO growth standards for school-aged children and adolescents’ for children up to age 5 years and older than 5 years, respectively (BMI-SDS). These types of growth profiles were analyzed as predictors for incident asthma. Three growth pattern classes were identified: a normative growth class, a class with early rapid growth up to 2 years of age, and a class with persistent rapid growth up to 6 years of age. Only very few earlier longitudinal studies have explicitly investigated whether the type of BMI development affects incident asthma in early childhood, and no previous study has applied a latent class growth mixture model. This type of model was applied by Rzehak *et al.* and allowed the identification of different types of time-varying growth processes of BMI development over the whole study period within the heterogeneity of individually varying trajectories. Children with a rapid BMI-SDS gain in the first 2 years of life had a higher risk for incident asthma up to age 6 years compared with children with a less pronounced weight gain slope in early childhood. The hazard ratio was 1.3 (95% CI: 1.1–1.5) after adjustment for birth weight, weight-for-length at birth, gestational age, sex, maternal smoking in pregnancy, breastfeeding, and family history of asthma or allergies. A rapid BMI gain at 2–6 years of age in addition to a rapid gain in the first 2 years of life did not significantly enhance the risk of asthma.

Three recent reviews have confirmed an association between asthma and obesity [7^{***}, 8^{***}, 9], and two of them performed a meta-analysis on six prospective cohort studies conducted in children. Of the studies included [10–15] in the meta-analysis by Chen *et al.* [7^{***}], two [13, 14] were the same as in the meta-analysis by Egan *et al.* [8^{***}], and four were new [16–19]. The meta-analysis by Chen *et al.* [7^{***}] reported a combined result of relative risk (RR) of incident asthma for overweight children as compared with nonoverweight children (RR: 1.19; 95% CI: 1.03–1.37). The relationship was further elevated for obesity vs. nonobesity (RR: 2.02; 95% CI: 1.16–3.50). A dose-responsiveness of elevated BMI on asthma incidence was observed (P for trend, 0.004). The meta-analysis by Egan *et al.* [8^{***}] showed a combined RR of obesity associated with asthma in both boys and girls (RR: 1.50; 95% CI: 1.22–1.83), in boys only (RR: 1.40; 95% CI: 1.01–1.93), and in girls only (RR: 1.53; 95% CI: 1.09–2.14). Sex seemed to be a significant modifier of the strength of the relationship between overweight/obesity in childhood and incident asthma only in the meta-analysis by Chen *et al.* [7^{***}]. Obese boys had a significantly larger effect than obese girls. No such effect was seen in the meta-analysis by Egan *et al.* [8^{***}].

CONCLUSION

The prospective cohort studies included in the two recently published meta-analyses found an association between overweight (and especially obesity) and asthma in the appropriate temporal sequence and in a dose–response manner. A statistically significant dose–response relationship between BMI and asthma incidence was observed, and strengthened the notion of a causal relationship. Whether this association is indeed causal is beyond the scope of this review of epidemiological studies. There was contradictory evidence of effect modification by sex, ethnicity, and age. Whereas the study by Lee *et al.* [10] found a protective effect of weight on asthma risk in girls, the opposite was seen in the study by Black *et al.* [5]. This latter study was also the only one to consider effect modification by ethnicity. Regarding age, the BAMSE study indicated that a high BMI during the first 4 years of life did not increase the risk of asthma at school age among children who had developed a normal weight by age 7 years. These results are inconsistent with those from the GINIplus/LISAplus study from Germany [2], potentially because of the higher time resolution of anthropometric measurements in GINIplus/LISAplus during the first months of life, whereas BAMSE had anthropometric data at age 1, 4, and 7 years. Consistently with GINIplus/LISAplus, the eight European Birth Cohorts – (GA²LEN) [6[■]] showed the strongest association with asthma among children with a rapid BMI-SDS gain in the first 2 years of life. These children had a higher risk for asthma within the first 6 years of life compared with children with a less pronounced weight gain slope in early life. The gain in BMI over time during infancy may be an even more important predictor for asthma in childhood than excess weight at any specific age.

Acknowledgements

None.

Conflicts of interest

There are neither conflicts of interest nor external funding.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Magnusson JO, Kull I, Mai XM, *et al.* Early childhood overweight and asthma and allergic sensitization at 8 years of age. *Pediatrics* 2012; 129:70–76.
2. Flexeder C, Thiering E, Bröske I, *et al.* Growth velocity during infancy and onset of asthma in school-aged children. *Allergy* 2012; 67:257–264.
3. Noal RB, Menezes AM, Macedo SE, *et al.* Is obesity a risk factor for wheezing among adolescents? A prospective study in southern Brazil. *J Adolesc Health* 2012; 51:S38–S45.
4. Anderson EL, Fraser A, Martin RM, *et al.* Associations of postnatal growth with asthma and atopy: the PROBIT Study. *Pediatr Allergy Immunol* 2013; 24:122–130.
5. Black MH, Zhou H, Takayanagi M, *et al.* Increased asthma risk and asthma-related healthcare complications associated with childhood obesity. *Am J Epidemiol* 2013; 178:1120–1128.
6. Rzehak P, Wijga AH, Keil T, *et al.* Body mass index trajectory classes and incident asthma in childhood: results from 8 European Birth Cohorts – a Global Allergy and Asthma European Network initiative. *J Allergy Clin Immunol* 2013; 131:1528–1536.
- A combined analysis of eight prospective longitudinal studies that investigated whether the type of BMI development affects incident asthma in early childhood by applying a latent class growth mixture model.
7. Chen YC, Dong GH, Lin KC, Lee YL. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis. *Obesity Rev* 2013; 14:222–231.
- Sex seemed to be a significant modifier of the strength of the relationship between overweight/obesity in childhood and incident asthma only in the meta-analysis.
8. Egan KB, Ettinger AS, Bracken MB. Childhood body mass index and subsequent physician-diagnosed asthma: a systematic review and meta-analysis of prospective cohort studies. *BMC Pediatr* 2013; 13:121.
- This systematic review provides a good assessment of the prospective studies evaluating the association between overweight/obesity and subsequent physician-diagnosed asthma in childhood.
9. Papoutsakis C, Priftis KN, Drakouli M, *et al.* Childhood overweight/obesity and asthma: is there a link? A systematic review of recent epidemiologic evidence. *J Acad Nutr Diet* 2013; 113:77–105.
10. Lee YL, Chen YC, Chen YA. Obesity and the occurrence of bronchitis in adolescents. *Obesity* 2012. doi: 10.1038/oby.2012.178. [Epub ahead of print]
11. Tollefsen E, Langhammer A, Romundstad P, *et al.* Female gender is associated with higher incidence and more stable respiratory symptoms during adolescence. *Respir Med* 2007; 101:896–902.
12. Burgess JA, Walters EH, Byrnes GB, *et al.* Childhood adiposity predicts adult-onset current asthma in females: a 25-yr prospective study. *Eur Respir J* 2007; 29:668–675.
13. Mannino DM, Mott J, Ferdinands JM, *et al.* Boys with high body masses have an increased risk of developing asthma: findings from the National Longitudinal Survey of Youth (NLSY). *Int J Obes* 2006; 30:6–13.
14. Gilliland FD, Berhane K, Islam T, *et al.* Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol* 2003; 158:406–415.
15. Chinn S, Rona RJ. Can the increase in body mass index explain the rising trend in asthma in children? *Thorax* 2001; 56:845–850.
16. Gold DR, Damokosh AI, Dockery DW, Berkey CS. Body-mass index as a predictor of incident asthma in a prospective cohort of children. *Pediatr Pulmonol* 2003; 36:514–521.
17. Ho WC, Lin YS, Caffrey JL, *et al.* Higher body mass index may induce asthma among adolescents with preasthmatic symptoms: a prospective cohort study. *BMC Public Health* 2011; 11:542.
18. Mamun AA, Lawlor DA, Alati R, *et al.* Increasing body mass index from age 5 to 14 years predicts asthma among adolescents: evidence from a birth cohort study. *Int J Obes* 2007; 31:578–583.
19. Zhang Z, Lai HJ, Roberg KA, *et al.* Early childhood weight status in relation to asthma development in high-risk children. *J Allergy Clin Immunol* 2010; 126: 1157–1162.