Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 European children

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Background: Preterm birth, low birth weight, and infant catch-up growth seem associated with an increased risk of respiratory diseases in later life, but individual studies showed conflicting results.
Objectives: We performed an individual participant data meta-analysis for 147,252 children of 31 birth cohort studies to determine the associations of birth and infant growth characteristics with the risks of preschool wheezing (1-4 years) and school-age asthma (5-10 years).
Methods: First, we performed an adjusted 1-stage random-effect meta-analysis to assess the combined associations of gestational age, birth weight, and infant weight gain with childhood asthma. Second, we performed an adjusted 2-stage random-effect meta-analysis to assess the associations of preterm birth (gestational age <37 weeks) and low birth weight (<2500 g) with childhood asthma outcomes.
Results: Younger gestational age at birth and higher infant weight gain were independently associated with higher risks of preschool wheezing and school-age asthma ($P < .05$). The inverse associations of birth weight with childhood asthma were explained by gestational age at birth. Compared with term-born children with normal infant weight gain, we observed the highest risks of school-age asthma in children born preterm with high infant weight gain (odds ratio [OR], 4.47; 95% CI, 2.58-7.76). Preterm birth was positively associated with an increased risk of preschool wheezing (pooled odds ratio [pOR], 1.34; 95% CI, 1.25-1.43) and school-age asthma (pOR, 1.40; 95% CI, 1.18-1.67) independent of birth weight. Weaker effect estimates were observed for the associations of low birth weight adjusted for gestational age at birth with preschool wheezing (pOR, 1.10; 95% CI, 1.00-1.21) and school-age asthma (pOR, 1.13; 95% CI, 1.01-1.27).
Conclusion: Younger gestational age at birth and higher infant weight gain were associated with childhood asthma outcomes. The associations of lower birth weight with childhood asthma were largely explained by gestational age at birth. (J Allergy Clin Immunol 2014;133:1317-29.)

Key words: *Gestational age, low birth weight, infant growth, wheezing, asthma, children, cohort studies, epidemiology*

Respiratory diseases have at least part of their origins in early life. It has been hypothesized that adverse exposures in fetal and early postnatal life might influence lung growth and development, which could lead to persistently smaller airways and impaired lung function. These developmental adaptations might predispose the subject to asthma and chronic obstructive pulmonary disease in childhood and adulthood.[1-3] This hypothesis is supported by studies showing associations of low birth weight with an increased risk of wheezing and asthma in childhood[4-7] and chronic obstructive pulmonary disease and lower pulmonary function in later life.[8-11] Published findings are not consistent,[4-7,12,13] which might be due to differences in study populations and in definitions of outcomes. Also, the observed associations of low birth weight with an increased risk of asthma-related outcomes might be confounded by preterm birth or catch-up growth in infancy. The lungs of preterm children have not yet been fully developed, which makes them prone to suboptimal further development.[14-16]

Most children with low birth weight show catch-up growth in infancy.[17] Recent studies suggested that catch-up growth is associated with lower pulmonary function and an increased risk of

Abbreviations used
BMI: Body mass index
ISAAC: International Study on Asthma and Allergy in Childhood
OR: Odds ratio
pOR: Pooled odds ratio
SDS: Standard deviation scores

childhood asthma.[18-20] Whether and to what extent the previously reported associations of low birth weight with higher risks of asthma-related outcomes are explained by preterm birth and infant catch-up growth is not known.

Therefore we conducted a meta-analysis of individual data from 147,252 children up to the age of 10 years participating in 31 European cohort studies to assess the strength, consistency, and independence of the associations of gestational age, birth weight, and infant weight gain with the risk of preschool wheezing and school-age asthma. We specifically explored the combined effects of gestational age, birth weight, and infant growth.

METHODS

Inclusion criteria and participating cohorts

European population-based birth and mother-child cohorts participated if they included children born between 1989 and 2011, had information available on at least gestational age and weight at birth and preschool wheezing (1-4 years) or school-age asthma (5-10 years), and were willing and able to exchange original data. We identified 52 European cohorts selected from the existing collaborations on childhood health or asthma-related outcomes (www.chicosproject.eu, www.birthcohortsenrieco.net,

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Supported by the European Community's Seventh Framework Programme FP7/2007-2013, project CHICOS. The research leading to these results has received funding from the European Respiratory Society and the European Community's Seventh Framework Programme FP7/2007-2013–Marie Curie Actions under grant agreement RESPIRE, PCOFUND-GA-2008-229571.

Disclosure of potential conflict of interest: I. Annesi-Maesano has received one or more grants from or has one or more grants pending with UE. S. H. Arshad has been supported by one or more grants from the National Institute of Health and Asthma UK and has received one or more payments for lecturing from or is on the speakers' bureau for Thermo Fisher and GlaxoSmithKline. H. Bisgaard has been supported by one or more grants from the Danish State Budget and the Lundbeck Foundation, has consultancy arrangements with Chiesi Pharmaceuticals, and has received one or more grants from or has one or more grants pending with the Danish Strategic Research Council, the Capital Region of Denmark, the Oticon Foundation, the European Research Council, and the Danish Council for Independent Research, Medical Sciences. C. Dogaru and C. E. Kuehni are employed by the University of Bern. M. Eggesbø has been supported by one or more grants from and has received support for travel from Chicos. A. J. Henderson has been supported by one or more grants from the Wellcome Trust and the Medical Research Council. H. M. Inskip has been supported by one or more grants from the UK Medical Research Council and many funding bodies and is a Board member for the UK Medical Research Council. T. Keil has received one or more grants from or has one or more grants pending with the European Commission. K. Lancz and L. Palkovicova have been supported by one or more grants from the NIH (NCI and Fogarty), the European Union, and the Slovak Ministry of Health. S. Lau has been supported by one or more grants from the German Research Foundation DFG, is a member of the Merck Drug monitoring committee, has consultancy arrangements with Allergopharma (Reinbek, Germany), has received one or more grants from or has one or more grants pending with Symbiopharm (Herborn, Germany), and has received one or more payments for lecturing from or is on the speakers' bureau for Symbiopharm, GlaxoSmithKline, CSL Behring. M. Mommers has been supported by one or more grants from the Netherlands Asthma Foundation and has received support for travel from the European Community Seventh Framework Programme. K. C. Pike has been supported by one or more grants from FSA BLF and has received various travel grants and bursaries, most recently from the European Respiratory Society. G. Roberts has been supported by one or more grants from the NIH and BMA. A. Schmidt has been supported by one or more grants from the Swiss National Science Foundation. C. Thijs has been supported by one or more grants from the Netherlands Asthma Foundation and has received support for travel from European Community's Seventh Framework Programme. M. Vrijheid has been supported by one or more grants from and has received support for travel from the European Community's Seventh Framework Programme FP7/2007-2013 (Project CHICOS). L. Duijts has received research support from the European Community's Seventh Framework Programme FP7/2007-2013 (Project CHICOS) and is the recipient of a European Respiratory Society/Marie Curie Joint Research Fellowship (no. MC 1226-2009). The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 27, 2013; revised December 28, 2013; accepted for publication December 30, 2013.

Available online February 12, 2014.

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0091-6749/$36.00

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http://dx.doi.org/10.1016/j.jaci.2013.12.1082

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