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Variations in the prevalence of childhood asthma and wheeze in MeDALL cohorts in Europe

Eleonora P. Uphoff^{1,2}, Philippa K. Bird¹, Joseph Maria Antó³, Mikel Basterrechea^{4,5,6}, Andrea von Berg⁷, Anna Bergström⁸, Jean Bousquet⁹, Leda Chatzi¹⁰, Maria Pia Fantini¹¹, Amparo Ferrero^{4,12}, Ulrike Gehring¹³, Davide Gori¹¹, Joachim Heinrich¹⁴, Thomas Keil¹⁵, Inger Kull⁸, Susanne Lau¹⁶, Dieter Maier¹⁷, Isabelle Momas¹⁸, Silvia Narduzzi¹⁹, Daniela Porta¹⁹, Fanny Ranciere¹⁸, Theano Roumeliotaki¹⁰, Tamara Schikowski²⁰, Henriette A. Smit²¹, Marie Standl¹⁴, Jordi Sunyer³ and John Wright¹

Affiliations: ¹Bradford Institute for Health Research, Bradford, UK. ²Dept of Health Sciences, University of York, York, UK. ³Instituto de Salud Global Barcelona, Barcelona, Spain. ⁴CIBER Epidemiología y Salud Pública, Madrid, Spain. ⁵Subdirectorate of Public Health of Gipuzkoa, Basque Government, Dept of Health, Gipuzkoa, Spain. ⁶Health Research Institute BIODONOSTIA, Gipuzkoa, Spain. ⁷Dept of Pediatrics, Marien Hospital Wesel, Wesel, Germany. ⁸Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden. ⁹Centre Hôpital Universitaire de Montpellier, Montpellier, France. ¹⁰Dept of Social Medicine, University of Crete, Heraklion, Greece. ¹¹Dipartimento di Scienze Biomediche e Neuromotorie, Università degli Studi di Bologna, Bologna, Italy. ¹²FISABIO, Universitat de València–Universitat Jaume I, Joint Research Unit, Valencia, Spain. ¹³Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands. ¹⁴Institute of Epidemiology, Helmholtz Zentrum München, Munich, Germany. ¹⁵Social Medicine, Epidemiology and Health Economics, Charité Medical University, Berlin, Germany. ¹⁶Pediatric Pneumology and Immunology, Charité Medical University, Berlin, Germany. ¹⁷Biomax Informatics AG, Planegg, Germany. ¹⁸Université Paris Descartes, Paris, France. ¹⁹Dipartimento di Epidemiologia del SSR del Lazio, Rome, Italy. ²⁰Leibniz-Institut für umweltmedizinische Forschung, Heinrich Heine Universität, Düsseldorf, Germany. ²¹Julius Center for Health Sciences and Primary Care, Public Health, Health Technology Assessment, Medical Humanities, University Medical Center Utrecht, Utrecht, The Netherlands.

Correspondence: Eleonora P. Uphoff, Dept of Health Sciences, University of York, Seeborn Rowntree Building, York, YO10 5DD, UK. E-mail: noortje.uphoff@york.ac.uk

ABSTRACT While there is evidence for variations in prevalence rates of childhood wheeze and asthma between countries, longitudinal, individual-level data are needed to understand these differences. The aim of this study was to examine variations in prevalence rates of childhood asthma, wheeze and wheeze with asthma in Europe.

We analysed datasets from 10 MeDALL (Mechanisms of the Development of ALLergy) cohorts in eight countries, representing 26 663 children, to calculate prevalence rates of wheeze and asthma by child age and wheeze with asthma at age 4 years. Harmonised variables included outcomes parent-reported wheeze and parent-reported doctor-diagnosed asthma, and covariates maternal education, parental smoking, pets, parental asthma, doctor-diagnosed allergic rhinitis, doctor-diagnosed eczema and wheeze severity.

At age 4 years, asthma prevalence varied from 1.72% in Germany to 13.48% in England and the prevalence of wheeze varied from 9.82% in Greece to 55.37% in Spain. Adjusted estimates of the proportion of 4-year-old children with wheeze diagnosed with asthma remained highest in England (38.14%, 95% CI 31.38–44.90%) and lowest in Spain (15.94%, 95% CI 6.16–25.71%).

The large differences in prevalence rates of asthma, wheeze and wheeze with asthma at age 4 years between European cohorts may indicate that childhood asthma is more readily diagnosed in some countries while going unrecognised elsewhere.



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Large variations in childhood wheeze across Europe do not match large variations in diagnosed childhood asthma <http://ow.ly/eJQk30aPInr>

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Introduction

Global burden of disease

In the International Study of Asthma and Allergies in Childhood (ISAAC), the global prevalence of wheeze was estimated to be 11.6% for 6–7-year-old children and 13.7% for 13–14-year-old children for the period around 2001–2003 [1]. Wheeze is particularly prevalent in English-speaking and Western countries [2]. Far less data are available on international prevalence rates of doctor-diagnosed asthma in children. The ISAAC study estimated the global prevalence of parent-reported doctor-diagnosed asthma among 6–7-year-old children to be 10.8%, with lower rates in Northern and Eastern Europe (4.5%), and the highest rates in North America (20.0%) and Oceania (29.2%). This pattern was repeated in 13–14-year-old children, with figures suggesting a small increase with age of ~2% in most countries except for Western Europe (9.1% among 6–7-year-olds to 16.3% among 13–14-year-olds) [1].

Wheeze versus doctor-diagnosed asthma

Self-reported wheeze is often used as an indicator of asthma [1]. While wheeze and asthma frequently go hand-in-hand, wheeze is not a sufficient, nor a necessary symptom, for the diagnosis of asthma. Partly due to the highly variable expression of asthma, there is no uniform set of diagnostic criteria [3]. SPYCHER *et al.* [4] showed that only 2.9% of all children in the general population present with the combination of wheeze, atopy and bronchial hyperresponsiveness described as typical for asthma. In another study, 25.8% of young adults with asthma never experienced childhood wheeze and of the children with wheeze, 51.8% did not develop asthma [5]. If differences between prevalence rates of wheeze and asthma vary internationally, using wheeze as a proxy for asthma is problematic.

Gaps in the evidence

Despite evidence of varying prevalence rates, no international comparisons of wheeze in combination with doctor-diagnosed asthma by child age are available. The ISAAC survey only measures self-reported wheeze and asthma in two age groups consisting of different samples [1]. Studying these variations between countries could lead to a greater understanding of modifiable factors involved, *e.g.* relating to the environment or the diagnostic process. The MeDALL (Mechanisms of the Development of ALLergy) partnership provides individual-level, longitudinal data with harmonised measures of wheeze and doctor-diagnosed asthma across cohorts [6]. We aimed to examine variations in the prevalence of childhood asthma, wheeze and wheeze with asthma by child age in Europe.

Methods

We analysed cross-sectional differences in childhood asthma and wheeze by child age and wheeze with asthma at age 4 years in datasets from European cohorts with harmonised variables on asthma and wheeze. Data were requested from 13 MeDALL cohort studies [6]. Table 1 provides an overview of the 10 included cohorts, representing eight countries and a total sample of 26663 children. More information about the cohorts can be found in the ENRIECO database (www.enrieco.dk).

Measures

The MeDALL partnership has developed harmonised variables, including harmonised definitions of asthma and wheeze [7]. “Ever asthma” is defined by the question “Has your child ever been diagnosed by a doctor as having asthma?” and “ever wheeze” is captured by the question “Has your child ever had wheezing or whistling in the chest?” For BAMSE, LISAPLUS and GINIPLUS cohorts, only wheeze and doctor diagnosis of asthma in the past 12 months were available in the follow-ups analysed, and composite measures based on annual reports of wheeze and/or asthma were created where possible (supplementary table S1). A third outcome measure was constructed to capture the proportion of children whose parents reported wheeze at least once from birth until age 4 years and who were reported to be diagnosed with asthma by age 4 years.

Key covariates included maternal education (low/medium/high, cohort specific), parental smoking up to child age 4 years, pets in the household up to child age 4 years (dog and/or cat and/or other pets, cohort specific), parental ever asthma, ever doctor-diagnosed allergic rhinitis and ever doctor-diagnosed eczema.

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TABLE 1 Overview of included MeDALL birth cohorts

Cohort	Country	Period of recruitment	Sample size n [#]	Inclusion criteria [¶]	Exclusion criteria	Setting
BAMSE (The Stockholm Children Allergy and Environmental Prospective Birth Cohort Study)	Sweden	1994–1996	4089	Birth in the selected areas	Disabled infants, plan to move, language barrier	Three areas of Stockholm (urban and suburban)
BiB (Born in Bradford)	England	2007–2010	1716	Birth at reference hospital	Plan to move before birth	Bradford (largely urban)
GINIplus (German Infant Nutritional Intervention study plus influence of pollution and genetics on allergy development)	Germany	1995–1998	5991	Healthy full-term newborns of German descent	Severe illness newborn, pre-term birth, low birthweight, language barrier, maternal history of immune-related disease, long-term medication or drug/alcohol abuse	Munich (mostly urban), Wesel (mostly rural)
INMA (Childhood and Environment)						
Menorca	Spain	1997–1998	482	Birth at reference hospital	Language barrier, assisted reproduction, mother <16 years, multiple births	Menorca (mostly urban)
Valencia	Spain	2003–2005	855	Birth at reference hospital	Language barrier, assisted reproduction, mother <16 years, multiple births	Valencia (mostly urban)
Sabadell	Spain	2004–2007	772	Birth at reference hospital	Language barrier, assisted reproduction, mother <16 years, multiple births	Sabadell (mostly urban)
Gipuzkoa	Spain	2006–2008	406	Birth at reference hospital	Language barrier, assisted reproduction, mother <16 years, multiple births	Gipuzkoa (mostly urban)
LISApplus (Influence of lifestyle factors on the development of the immune system and allergies in East and West Germany plus the influence of traffic emissions and genetics)	Germany	1997–1998	3094	Healthy full-term newborns of German descent	Severe illness newborn, pre-term birth, low birthweight, language barrier, maternal history of immune-related disease, long-term medication or drug/alcohol abuse	Munich (mostly urban), Wesel (mostly rural), Leipzig (mostly urban), Bad Honnef (mostly rural)
MAS (Multicentre Allergy Study)	Germany	1990	1314	Birth at reference hospitals	Language barrier, complications at birth, pre-term birth, low birthweight	Berlin, Düsseldorf, Freiburg, Mainz, Munich (urban)
PARIS (Pollution and Asthma Risk: an Infant Study)	France	2003–2006	1549	Healthy newborns	Pre-term, low birthweight, intensive care treatment, language barrier	Paris and three suburbs (urban)
PIAMA (Prevention and Incidence of Asthma and Mite Allergy)	The Netherlands	1996–1997	3963	Usable screening questionnaire		Mix of rural, urban, suburban
RHEA (Mother Child Cohort in Crete)	Greece	2007–2008	1336	Birth at reference hospitals	Mother ≤16 years, language barrier	Heraklion (island, mix of urban, suburban and rural)
ROBBIC (Rome and Bologna Birth Italian Cohorts)						
Co.N.ER (Bologna birth cohort)	Italy	2004–2005	434	Mother Italian citizen, birth at reference hospital	Language barrier, newborn moved hospital, mother ≤18 years	Bologna (urban)
GASPII (Gene and Environment: Prospective Study on Infancy in Italy)	Italy	2003–2004	694	Mother Italian resident	Language barrier, newborn moved hospital, mother ≤17 years	Rome (urban)

[#]: number of pregnant women or mothers as used in this study; [¶]: inclusion based on area of residence specified in last column.

Severity of wheeze was considered a potential explanatory variable in the relationship between cohort and percentage of children with wheeze diagnosed with asthma. However, as it was only available in five cohorts, it was used in additional analyses only. The measure was constructed from the question “How many attacks of wheezing has your child had in the last 12 months?” and coded low (0 times), medium or high severity (coding varied by cohort).

Statistical analysis

Prevalence rates of wheeze and asthma were calculated up to age 8 years, because four cohorts had no data from later time points (ROBBIC, RHEA, BiB and PARIS) and for many other cohorts a high loss to follow-up affected the reliability of the data (supplementary table S1).

Data for subcohorts in INMA and ROBBIC were pooled, although data availability differed across subcohorts for different time points (table 1). Cross-sectional logistic regression analyses were performed separately for outcomes asthma at age 4 years, wheeze at age 4 years and wheeze with diagnosed asthma at age 4 years. Unadjusted prevalence rates are presented by child age for all cohorts, and unadjusted and adjusted prevalence rates are presented for all cohorts at age 4 years, as this was the follow-up age with most data available across cohorts. Prevalence rates at age 4 years could not be calculated for the ROBBIC, MAS, GINIplus and LISApplus cohorts, because these studies did not measure the relevant outcomes at age 4 years.

Results

Characteristics of the cohort participants by cohort are described in supplementary table S2. Unadjusted prevalence rates and output from regression analyses are reported in supplementary table S3.

Prevalence rates of asthma and wheeze by child age

In all cohorts with longitudinal data, figure 1 suggests a trend for prevalence rates of asthma to increase with child age. Differences between prevalence rates at the first and last time point are statistically significant for each cohort (supplementary table S3). However, there were large differences between cohorts across the entire age range. Reported ever wheeze did not consistently increase with child age (figure 2).

Ever asthma at age 4 years

At age 4 years, for which eight cohorts provided data, unadjusted prevalence rates of ever asthma varied from 1.72% (95% CI 1.22–2.35%) in Germany (LISApplus) to 13.48% (95% CI 11.88–15.20%) in England (BiB) (figure 3).

Asthma at age 4 years was not associated with the presence of pets in the home (OR 1.02, 95% CI 0.88–1.18), but was associated with medium (OR 0.84, 95% CI 0.70–1.00) and high (OR 0.74, 95% CI 0.62–0.88) *versus* low maternal education, parental smoking (OR 1.31, 95% CI 1.10–1.57), parental asthma (OR 2.38, 95% CI 2.07–2.73), doctor-diagnosed allergic rhinitis (OR 4.12, 95% CI 3.23–5.25) and doctor-diagnosed eczema (OR 2.21, 95% CI 1.93–2.53).

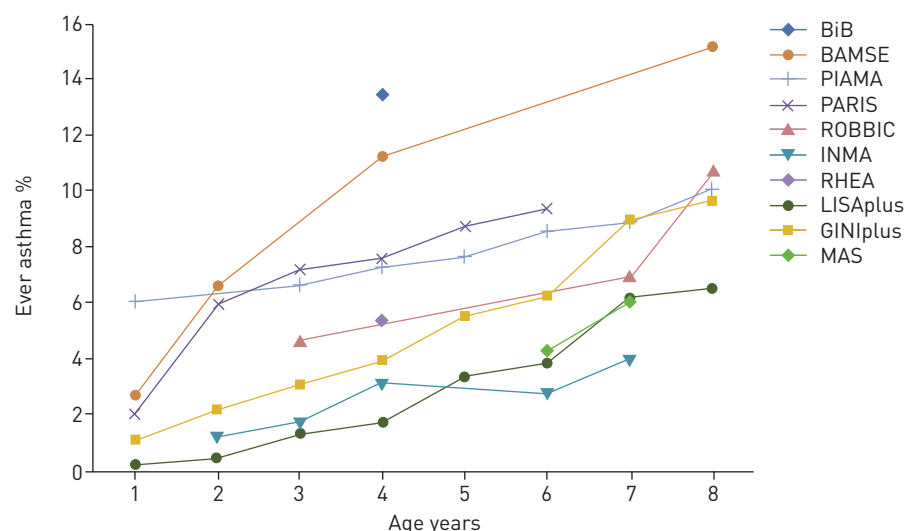


FIGURE 1 Prevalence rates of ever asthma by cohort (table 1) and child age.

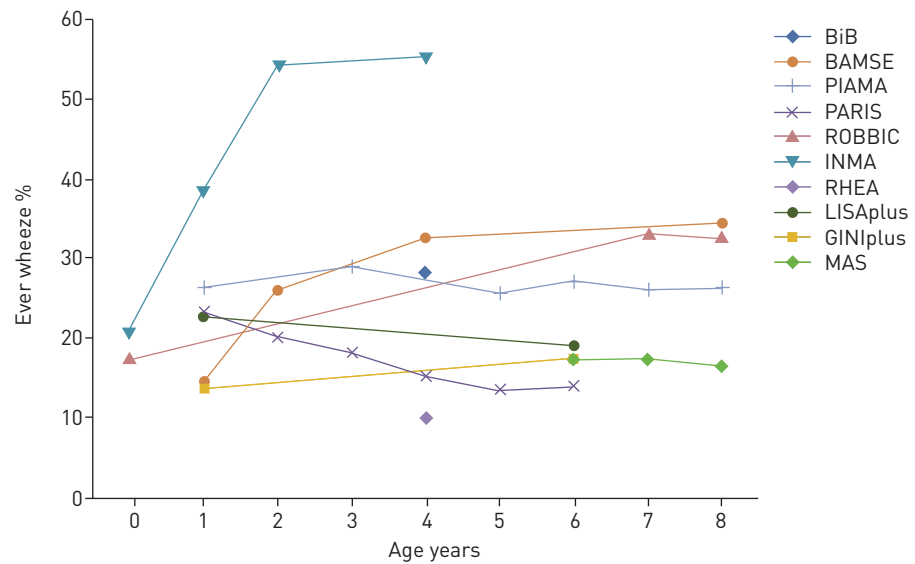


FIGURE 2 Prevalence rates of ever wheeze by cohort (table 1) and child age.

After adjusting for these covariates, prevalence rates shown in figure 3 indicate that large and consistent differences in diagnosed asthma at age 4 years remain. Again, the highest prevalence rates of asthma are found in England (BiB), Sweden (BAMSE) and France (PARIS), while Germany (GINIplus and LISApplus) and Spain (INMA) have the lowest rates.

Ever wheeze at age 4 years

There was a wide variation in prevalence rates of ever wheeze at age 4 years. However, cohorts with the highest average prevalence of asthma at age 4 years (figure 3) do not have the highest average prevalence of wheeze at age 4 years (figure 4). Unadjusted prevalence rates of wheeze at age 4 years for six cohorts with available data varied from 9.82% (95% CI 7.95–11.96%) in Greece (RHEA) to 55.37% (95% CI 52.21–58.51%) in Spain (INMA).

Wheeze at age 4 years was not associated with maternal education (OR 1.03, 95% CI 0.93–1.15 and OR 1.01, 95% CI 0.91–1.12 for low and medium *versus* high education, respectively) nor with pets in the home (OR 1.05, 95% CI 0.97–1.14), but was associated with parental smoking (OR 1.42, 95% CI

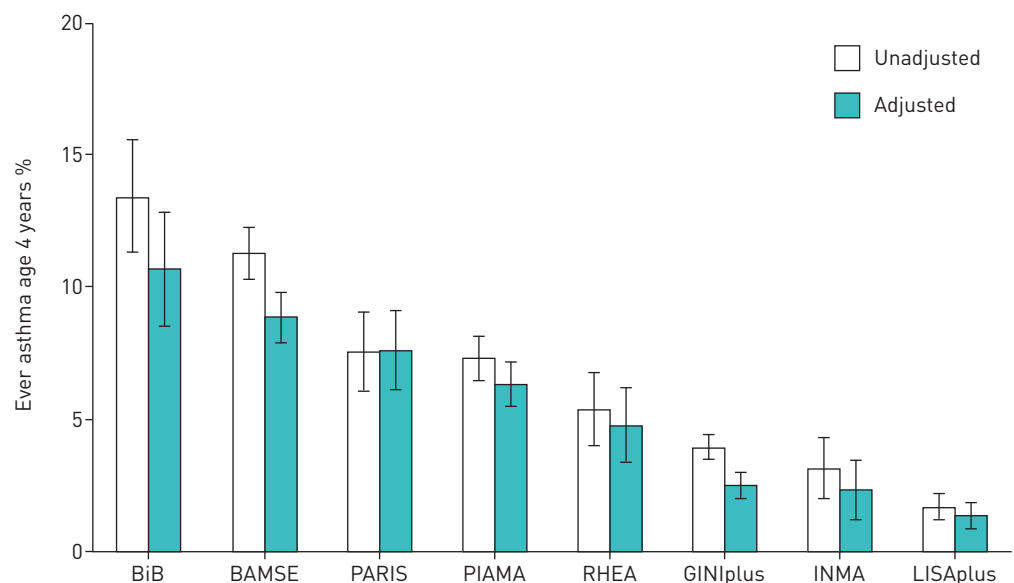


FIGURE 3 Unadjusted and adjusted prevalence rates of ever asthma at age 4 years by cohort (table 1).

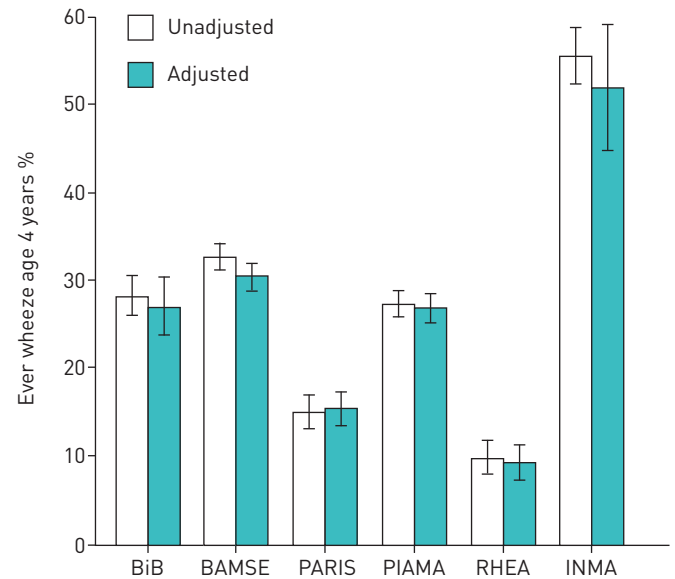


FIGURE 4 Unadjusted and adjusted prevalence rates of ever wheeze at age 4 years by cohort (table 1).

1.28–1.58), parental asthma (OR 1.71, 95% CI 1.57–1.87), doctor-diagnosed allergic rhinitis (OR 2.24, 95% CI 1.84–2.71) and doctor-diagnosed eczema (OR 1.52, 95% CI 1.40–1.65). Adjusted prevalence rates of wheeze remain highest in Spain (INMA), and lowest in France (PARIS) and Greece (RHEA) (figure 4).

Children with ever wheeze diagnosed with asthma by age 4 years

The proportion of children with ever wheeze who were diagnosed with asthma by age 4 years ranged from 15.94% (95% CI 8.24–26.74%) in Spain (INMA) to 39.53% (95% CI 35.07–44.12%) in England (BiB) (figure 5).

Wheeze with diagnosed asthma compared with wheeze without diagnosed asthma at age 4 years was not associated with low- *versus* medium-level maternal education (OR 0.83, 95% CI 0.65–1.05), but children with wheeze were less likely to be diagnosed with asthma if their mother had a low *versus* high level of education (OR 0.71, 95% CI 0.56–0.90). There was no association with parental smoking (OR 1.05, 95% CI 0.83–1.34) or pets (OR 1.01, 95% CI 0.82–1.24), but wheeze with asthma was more likely in children of parents with asthma (OR 1.85, 95% CI 1.52–2.24), children diagnosed with allergic rhinitis (OR 2.81, 95% CI 1.86–4.24) and children diagnosed with eczema (OR 1.68, 95% CI 1.40–2.03).

The probability of children with wheeze being diagnosed with asthma by age 4 years was also increased for medium *versus* low (OR 1.90, 95% CI 1.52–2.39) and high *versus* low wheeze severity (OR 5.65, 95% CI

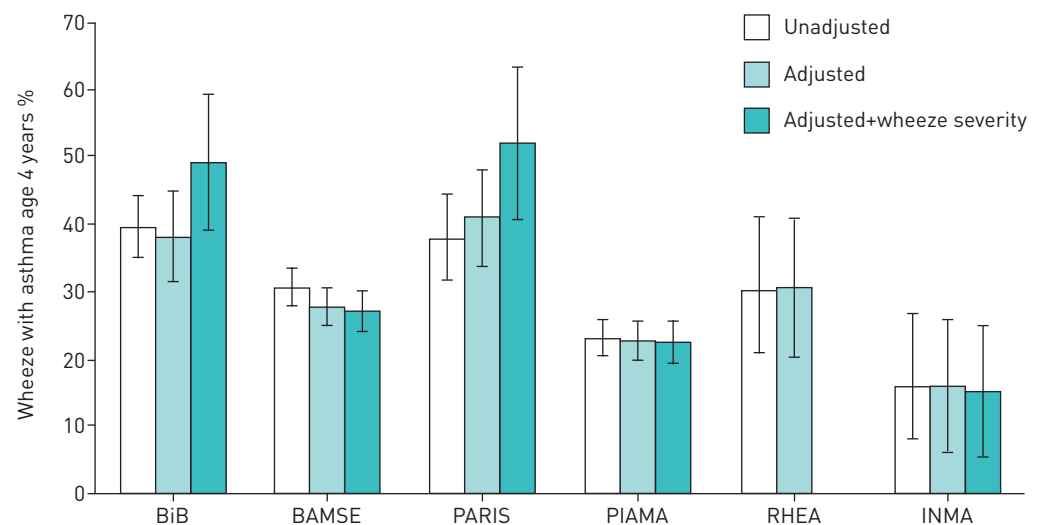


FIGURE 5 Prevalence rates of wheeze with diagnosed asthma at age 4 years by cohort (table 1).

4.24–7.54). However, adding wheeze severity to the model did not reduce between-cohort differences (figure 5). Estimates for children with wheeze diagnosed with asthma in the fully adjusted model were higher for England (BiB) (49.17%, 95% CI 39.17–59.18%) and France (PARIS) (52.07%, 95% CI 40.79–63.35%) than for Sweden (BAMSE) (27.06%, 95% CI 24.07–30.05%), the Netherlands (PIAMA) (22.49%, 95% CI 19.37–25.61%) and Spain (INMA) (15.31%, 95% CI 5.58–25.04%).

Discussion

Prevalence rates of childhood asthma and wheeze vary by country, with a seven-fold variation in asthma across cohorts at age 4 years and persisting differences at older ages. Whereas the prevalence of asthma generally increases with age, the prevalence of wheeze does not. The highest prevalence rates of asthma were found among cohorts in England, Sweden and France, and the lowest in Germany and Spain. The highest rates of wheeze were found in Spain, Italy and Sweden, and the lowest in Germany, France and Greece. Although we showed strong associations with covariates parental smoking, parental asthma, allergic rhinitis and eczema, these factors did not explain between-cohort differences in prevalence rates.

Discrepancies between prevalence rates of asthma and wheeze were confirmed by differences between cohorts in the proportion of children with wheeze diagnosed with asthma by age 4 years. Children with wheeze were more likely to be diagnosed with asthma if their mother had a higher level of education, if the child was diagnosed with allergic rhinitis or eczema and if wheeze was more severe. However, even after adjusting for these covariates, children with wheeze were more likely to be diagnosed with asthma in England and France than in Sweden, the Netherlands and Spain. We consider a few explanations for these variations.

Explaining variations between European cohorts

To put our findings in perspective, we compared our results with estimates from international surveys (supplementary appendix S1 and supplementary figure S1). Although no data on doctor-diagnosed childhood asthma were available, findings from two surveys among adults suggest findings in line with ours, with the highest prevalence rates of asthma in the UK, Sweden, France and the Netherlands, and consistently lower prevalence rates in Germany, Spain, Greece and Italy [8, 9]. Our estimates of wheeze in Spain and Italy are higher than previously found, but these cohorts are not representative of the general population (supplementary table S4).

Variations may be attributable to international differences in the diagnosis of childhood asthma or guideline adherence. The PRACTALL (Practical Allergy) consensus recommendations provide guidance for diagnosis and treatment of childhood asthma in Europe and North America, and state that suspected asthma can only be diagnosed through follow-up and a trial of treatment [10]. Current Dutch guidelines are even more cautious and discourage the diagnosis of asthma for children under the age of 6 years [11]. UK guidelines recommend a trial of treatment or watchful waiting for those under the age of 6 years, but state that more frequent and/or severe symptoms add certainty to the asthma diagnosis [12]. Swedish guidelines prioritise lung function and allergy tests even for those under the age of 4 years; in France, radiographs are recommended as standard practice [13, 14]. Furthermore, there are indications of underdiagnosis of childhood asthma, e.g. in Italy [15], and evidence of overdiagnosis in the Netherlands [16]. One study found that asthmatic complaints which often led to an asthma diagnosis for children in the Netherlands were frequently diagnosed and treated as bronchitis in Germany [17]. These differences in healthcare may contribute to some of the variation in prevalence rates of asthma and wheeze with diagnosed asthma found in our study.

Alternatively, limited access to healthcare and differences in the translation and interpretation of “wheeze” might play a role in various countries. The strength of the relationship between wheeze and asthma may also vary between countries. A recent study comparing childhood mortality rates found that the mortality rate for paediatric respiratory disorders in England was 6.6 times that of Sweden, despite the prevalence of childhood asthma being high in both countries [18].

Implications for research

Future research should aim to explain variations in childhood wheeze and diagnosed asthma in longitudinal analyses, e.g. in age–period–cohort analyses. This could determine whether rates of asthma in some countries are rising over time, rather than with age alone. We also suggest that, in addition to environmental factors such as air pollution and climate, international variations in diagnoses, access to healthcare and quality of care deserve consideration.

A second implication for research concerns the findings that, while the prevalence of childhood asthma increased with child age, wheeze did not. Wheeze is not a reliable indicator of asthma at an early age when many young children are yet to be diagnosed. The levelling in the prevalence of ever wheeze with

increasing child age suggests that these estimates are affected by recall bias. Parents may not remember transient wheeze suffered by their children at an early age if it does not progress to asthma. A previous version of the UK guidelines warned that “Parents often use ‘wheezing’ as a non-specific label ...” [12]. Using parent-reported wheeze as an indicator of asthma for young children therefore leads to overestimates of the prevalence of childhood asthma.

Implications for practice

Consensus recommendations have not yet led to an internationally uniform diagnosis of childhood asthma [10]. Our results suggest that the likelihood of children with asthma being diagnosed, and subsequently the quality of care, may vary internationally. We have shown that in many countries children are diagnosed with asthma at age 4 years or earlier, while it is doubtful whether a diagnosis of childhood asthma can be made with certainty at such a young age. It will take the joint effort of healthcare professionals and researchers to ensure the diagnosis of childhood asthma is uniform and accurate.

Limitations

As shown in table 1, cohorts used different inclusion and exclusion criteria, and participants were recruited from centres not representative of the general population. Limited generalisability is particularly problematic for cohorts using exclusion criteria related to the risk of asthma, such as mothers who do not speak the language of the country and infants with complications at birth [19–21]. This, in addition to variations in time periods of data collection and the limited availability of harmonised covariates at different follow-ups, means that comparisons of prevalence rates between cohorts and within cohorts over time should be made with caution. For example, composed outcome variables created for some cohorts were based on data from multiple time points, leading to overestimation. Despite the availability of data at multiple time points, our analysis was cross-sectional and measured asthma and wheeze “ever” rather than “in the last 12 months” due to data limitations. However, we believe our conclusions are strengthened by taking into account key covariates, by the fact that differences between cohorts persist at different child ages and that these generally correspond with results from other surveys.

Conclusions

There are differences in prevalence rates of childhood asthma and wheeze across Europe, which vary by child age. The proportion of children with wheeze who were diagnosed with asthma was higher among cohorts in England, Sweden and France than in the Netherlands and Spain, even when the higher proportion of severe wheeze in England and France was adjusted for. This may partly indicate that asthma is more readily diagnosed in some countries, while going unrecognised in others. Given the burden on patients and healthcare associated with overdiagnosis as well as underdiagnosis, the discussion on diagnostic criteria for asthma should be an international one.

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