How did the study come about?
Childhood asthma resembles a complex syndrome rather than a single disease. Clinical manifestations include cough, shortness of breath and wheeze.1 Because of its high prevalence, it is of major public health relevance.2,3 Presentation and disease course of childhood wheezing disorders vary,4 and its phenotypes are difficult to distinguish in early childhood despite the demand for diverse therapeutic strategies.5 Current treatments have no sustained effect on development of lung function and cannot prevent tracking of reduced lung function.6 Risk factors for childhood wheeze and subsequent asthma include genes, environmental factors and their interaction:1,7,8 all these affect lung development directly or indirectly (Figure 1). Data on the association between lung development and respiratory symptoms9 in early childhood are mostly derived from small hospital-based studies. Larger epidemiological studies have been based on questionnaires and most studies have been conducted in older children,2 in high-risk populations10 or retrospectively.11 There is a lack of prospectively assessed lung function studies in unselected healthy infants that take into account genetic and environmental factors. However, in order to disentangle the complex interaction of these predisposing factors on lung development and childhood wheeze, relatively large groups of infants need to be studied, with repeated lung function measurements, assessment of environmental and hereditary factors and clinical outcomes. The ‘Bern Infant Lung Development’ (BILD) cohort aims to contribute towards closing this gap. It was set up in 1999 to study physiological properties of the respiratory system and environmental and genetic risk factors affecting lung development in healthy individuals from infancy through childhood in relation to wheeze.9

How is it funded?
Direct costs of the cohort are being paid by project grants from the Swiss National Science Foundation, the European Respiratory Society (ERS), the Austrian, German and Swiss Paediatric Respiratory Society and Swiss Governmental Anti-Tobacco Fund. The University Children’s Hospital in Bern, Switzerland, where the study centre is located, provides the infrastructure. All studies were approved by the local Ethics Research Committee.

What does it cover?
In a comprehensive approach, we search for early markers of common respiratory morbidity, including respiratory infections and asthma, by trying to disentangle predisposing and modifying factors of respiratory morbidity within the context of lung development. This includes the assessment of immune development and markers of airway inflammation in response to environmental triggers.

The strengths of the BILD cohort are its hallmarks: the prospective approach with standardized data collection starting before birth in unselected children; the accurate and standardized measurements of lung function and markers of airway inflammation; and the detailed assessment of incidence and determinants of respiratory symptoms especially during the first year of life.12 To explain developing properties of lung and airways during the vulnerable phases, lung function is measured at the age of 1 month and at the age of 6 years, with further lung function measurements planned for the age of 12 years.

We study the complex reaction of lung and airways to environmental triggers, which is possibly
influenced both by inflammation and immune response. Here, we measure the association between exposure to environmental tobacco smoke (ETS), air pollution and lung function, markers of airway inflammation and components of the immune system. In addition, we prospectively assess viral pathogens of lower respiratory tract infections during the first year of life, as well as related respiratory symptoms and their severity.

Data covering genetic risk factors for childhood asthma are rapidly increasing. However, little is known about their effect on lung development and childhood wheeze. This is particularly true for genes known, from animal models, to be involved in lung development. Therefore, we measure the effect of single-nucleotide polymorphisms in these genes in comparison with genes associated with clinical manifestation of childhood allergy, asthma or wheeze.

**Who is in the sample?**

Recruitment for the BILD cohort is ongoing; about 35 unselected healthy neonates enter the cohort every year. Study participants are born after April 1999 in the agglomeration of Bern, the capital of Switzerland. One-third of the study population comes from the rural surroundings, and two-thirds from the urban area of Bern, which still offers relatively rural living conditions compared with other European cities.

Pregnant mothers are recruited at the four major maternity hospitals and practices of obstetricians in the agglomeration of Bern through advertisements and interviews. Interested families receive informative letters describing involved measurements and are contacted by the study centre. The following inclusion criteria apply: White ethnicity, term delivery (at least 37 weeks), ability of parents to speak one of the major Swiss languages (German, French), no severe maternal health problems, no maternal drug abuse other than nicotine, no known major birth defects or perinatal disease of the newborn, such as respiratory distress, airway malformation or other major respiratory diseases diagnosed after birth.

From 1999 until the end of 2009, a total of 42 110 mothers gave birth at the four major maternity hospitals in the agglomeration of Bern. By the end of 2009, we recruited 364 study participants (see Table 1 for anthropometric data of infants with lung function data), and 107 have been followed-up so far at the age of 6 years (Table 2). The others have not yet reached this age.

**Table 1** Anthropometric data of study participants in the BILD cohort with information on lung function ($N=344$) at the age of 1 month

| Anthropometric data                  | Median | Interquartile range | Range  |
|-------------------------------------|--------|---------------------|--------|
| Gestational age at birth (weeks)    | 39.9   | 38.9–40.6           | 37.0–42.3 |
| Birth weight (g)                    | 3410   | 3060–3660           | 2170–4915 |
| Age at study date (weeks)           | 5.0    | 4.6–5.4             | 3.6–8.3 |
| Weight at study date (g)            | 4325   | 4010–4750           | 2890–6400 |
| Length at study date (cm)           | 54.6   | 53.1–56.5           | 48.0–61.5 |

**Table 2** Number of participants initially recruited, number completing study Phases 1 and 2 and number of drop-outs during study Phases 1 and 2 from 1999–2009 in the BILD cohort

| Year | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | Total until 31/12/2009 |
|------|------|------|------|------|------|------|------|------|------|------|------|------------------------|
| Prenatally recruited                | 26    | 40   | 20   | 21   | 46   | 44   | 37   | 29   | 30   | 45   | 25   | 364                    |
| Completed study phase 1             | 23    | 37   | 19   | 20   | 45   | 44   | 36   | 28   | 29   | 44   | 25   | 350                    |
| Completed study phase 2             | –     | –    | –    | –    | –    | –    | –    | –    | 28   | 14   | 11   | 18    | 36    | 107            |
| Drop-outs during study phase 1      | 3     | 3    | 1    | 1    | 1    | 0    | 1    | 1    | 1    | 1    | 1    | 14                          |
| Drop-outs after study phase 1       | –     | –    | –    | –    | –    | –    | 8    | 8    | 7    | 1    | 8    | 32                          |
How often have they been followed-up? What is attrition like?

The study design of the BILD cohort is shown in Figure 2. It includes three study phases with three questionnaires, weekly telephone interviews during the first year of life, two visits to the study centre and two visits to the families’ homes at the time of the first lower respiratory infection.

Study Phase 1 starts with recruitment. After birth, midwives extract perinatal history from medical records, and take cord blood and first urine samples if eligibility is confirmed. At the age of 1 month, the infants visit the study centre. On this occasion, lung function measurements and maternal skin-prick tests are performed, and Questionnaire 1 is used to assess pre- and perinatal history including family and maternal past medical history. Questionnaires 2 and 3 assess the study participant’s history during Phase 2. While

Attrition was low during Phase 1 and relatively low during Phase 2. We lost only 13 of 364 recruited infants (3.7%) during Phase 1 and only 31 of 138 children (22.5%) during Phase 2 (Table 2). Drop-outs were almost exclusively due to personal reasons (8 during Phase 1, 25 during Phase 2), and to families moving away (1 during Phase 1, 5 during Phase 2). Five children were excluded because of heart disease diagnosed after the neonatal period (four in Phase 1 and one in Phase 2).

What has been measured?

The data are derived from four sources: (i) hospital records; (ii) questionnaires; (iii) telephone interviews; and (iv) objective measurements. A detailed description of data collected in the BILD cohort during Phases 1 and 2 is given in Table 3.

Hospital records (i): these are used to extract information about maternal warning signs during the delivery and perinatal history. During the first year of life, study nurses perform regular weekly telephone calls with standardized interviews.

After the first year of life, Study Phase 2 starts. The first follow-up is performed at the age of 6 years, when participants visit the study centre to undergo lung function measurements and skin-prick tests. Questionnaires 2 and 3 assess the history during Study Phase 2. A further follow-up as part of Study Phase 3, also including lung function measurements and skin-prick tests, is planned for the age of 12 years.

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| Data collection from hospital records, questionnaires and telephone interviews | Study Phase 1 (pregnancy until age 1 year) | Study Phase 2 (age 1 year until age 6 years) |
|---|---|---|
| **General health condition** | Source: hospital records | Source: Questionnaires 2 and 3 |
| Maternal warning signs during delivery | | Common colds, infections (especially upper and lower respiratory tract, ear, nose, throat), number and duration |
| Amount, quality of amniotic fluid, aspiration of amniotic fluid, colour of amniotic fluid (meconium) | | Atopic rhinitis or conjunctivitis, seasonality of symptoms, months of occurrence, effect of symptoms on indoor and outdoor activities, hay fever |
| Weight and quality of placenta | | Asthma, severity; triggers, number and severity of attacks; nocturnal/diurnal, doctor-diagnosed asthma, Atopic dermatitis |
| Premature rupture of membranes | | Behavioural problems, enuresis (primary, secondary, diurnal, nocturnal) |
| Infection, antibiotics, chorioamnionitis | | Medication, paracetamol 12 months prior to follow-up |
| Perinatal warning signs | | Level and impairment of indoor and outdoor activity, type of activity, indoor swimming |
| Apnoea, tachypnea, bradycardia, cyanosis, expiratory groaning, signs of dyspnea, bradycardia, abnormality cardiotocogram | | Medications 12 months prior to follow-up, alternative medications and remedies used |
| pH measured in blood from umbilical vein and artery, acidosis or alkalosis | | |
| **Respiratory symptoms** | Source: weekly telephone interviews during first year of life$^{52,53}$ | Source: Questionnaires 2 and 3 |
| Respiratory symptoms (including cough and wheeze during day and night, difficulty breathing, feeding difficulties, reduced activity) | | Cough, type of cough, cough without infection, triggers of cough, cough severity, subjective assessment of first time of cough, last time of cough, duration free of cough during 12 months prior to follow-up, seasonality of cough, months of occurrence |
| Using standardized score to group symptoms into four levels according to severity and with high sensitivity for lower respiratory-tract infections | | Audible wheeze, triggers of wheeze, nocturnal, diurnal, subjective assessment of first time of wheeze, last time of wheeze, seasonality of wheeze, months of occurrence |
| Main outcome parameter: weeks with severe respiratory symptoms (defined as total number of weeks with day or night score of $\geq 3$) | | Rales or rhonchi, triggers of rales, rhonchi, nocturnal, diurnal |
| **Environmental exposures** | Source: Questionnaire 1, weekly telephone interviews during first year of life$^{52,53}$ | Source: Questionnaires 2 and 3 |
| Pets and exact type of pet at home, during/after pregnancy | | Snoring, sleep disturbance, tonsillectomy |
| Pets given away due to allergy/atopy in family | | |
| Farming exposure, animal type | | |
| Traffic exposure at home (trucks) | | |
| Type of heating, type of stove, chimney, open fire place | | |
| Sleeping environment child (mattress, encasement, sheepskin rug use) | | |
| Damage due to damp at home, assessment of exposure to mould | | |
| Maternal active or passive smoking, ETS exposure, number of cigarettes, smoking cessation, coffee/tea and number of cups, caffeine containing soft drinks, vitamin supplement intake, fruit intake, antibiotics, steroid treatment, respiratory infections, gastrointestinal infections, urinary tract | | |
| (continued) | | |
Table 3 Continued

| Data collection from hospital records, questionnaires and telephone interviews | Study Phase 1 (pregnancy until age 1 year) | Study Phase 2 (age 1 year until age 6 years) |
|---|---|---|
| | infections, vaginitis, colpitis, worm infections, other infections during pregnancy and during first year of life | cessation until first major follow-up at the age of 6 years |
| Paternal active smoking, number of cigarettes, smoking cessation during pregnancy and first year of life | | |

**Objective measurements**

| Study Phase 1 (pregnancy until age 1 year) | Study Phase 2 (age 1 year until age 6 years) |
|---|---|
| Measurements of lung function and inflammation of airways | Tidal breathing measurements
Unsedated infants, during quiet natural sleep
Ultrasonic flowmeter (Spiroson®, EcoMedics AG, Duernten, Switzerland) with infant face mask
Main outcome parameters: minute ventilation (tidal volume multiplied by respiratory rate) and expiratory flow
Measurement of fraction of exhaled nitric oxide (FeNO)
Rapid-response chemoluminescence analyzer (CLD 88, EcoMedics AG, Duernten, Switzerland), with a range of 0–100 parts per billion (ppb), infant face mask
Breath-by-breath measurement
Main outcome parameter: mean FeNO
Multiple Breath Washouts (Sulfurhexafluoride)
Ultrasonic flowmeter (see above), infant face mask
Main outcome parameters: lung volume (FRC) and ventilation inhomogeneity (LCI)
Interrupter resistance measurement
Ultrasonic flowmeter (see above), shutter box, infant face mask
Main outcome parameter: Rint
Anthropometric data at study date: body weight and length, head circumference |

Skin-prick test | Maternal skin-prick test
Dog dander, cat dander, Dermatophagoides pteronyssinus, mixed tree pollens, mixed grass pollens, Alternaria tenuis, positive control (histamine), negative control (NaCl), Allergomed, Switzerland |

Immunology | Specimen: cord blood
Haematocrite, haemoglobin count, white blood cell count, leucocyte subtypes
Total IgE, eosinophil cationic protein, eosinophil protein X, interleukin subtypes, interferon subtypes |

(continued)
### Table 3

#### Objective measurements

| Study Phase 1 (pregnancy until age 1 year) | Study Phase 2 (age 1 year until age 6 years) |
|------------------------------------------|---------------------------------------------|
| **Objective** | **Measurements** |
| Mannose-binding lectin (MBL) measured as described previously with commercially available ELISA kits (Antibodyshop, Gentofte, Denmark) | DNA extraction from mucosa cells retrieved per buccal swabs or from saliva collection |
| **Study Phase 1** | **Study Phase 2** |
| Specimen: anterior nasal swabs | Analysis of SNPs and Analysis of copy number variants in genes involved in lung growth per DNA chip analysis |
| Taken at any first acute respiratory infection, which is defined as >2 days with cough or wheeze, together with fever >38°C, acute rhinitis, otitis media or pharyngitis; specimens are analysed by polymerase chain reaction (PCR) based assays, e.g. Taqman real-time PCR, targeting 16 different respiratory viruses commonly infecting humans | DNA extraction from mucosa cells retrieved per buccal swabs or from saliva collection |
| **Study Phase 2** | **Study Phase 2** |
| Specimen: first urine after birth and urine during first lower respiratory-tract infection | Analysis of SNPs and Analysis of copy number variants in genes involved in lung growth per DNA chip analysis |
| Nicotine and cotinine | DNA extraction from mucosa cells retrieved per buccal swabs or from saliva collection |
| Caffeine | DNA extraction from mucosa cells retrieved per buccal swabs or from saliva collection |
| **Air pollution at community level** | **Air pollution at individual level** |
| Swiss National Air Pollution Monitoring Network (Nationales Beobachtungsnetz für Luftverunreinigungen, NABEL) measurement sites | Swiss NABEL measurement sites |
| Daily mean levels of particulate matter with aerodynamic diameter of <10 μm (PM10) | Daily mean levels of PM10 |
| Daily mean levels of nitrogen dioxide (NO2) | Daily mean levels of NO2 |
| Daily maximum of mean hourly levels of ozone (O3) | Daily maximum of mean hourly levels of O3 |
| Stationary passive samplers (Palmes Tubes) at measurement sites: daily mean levels of NO2 | Stationary passive samplers (Palmes Tubes) at measurement sites: daily mean levels of NO2 |
| **Air pollution at individual level** | **Air pollution at individual level** |
| Mobile passive samplers: daily mean levels of PM2.5 and PM10 | Mobile passive samplers: daily mean levels of PM2.5 and PM10 |
| Stationary passive samplers (Palmes Tubes) at study participants’ homes: daily mean levels of NO2 | Stationary passive samplers (Palmes Tubes) at study participants’ homes: daily mean levels of NO2 |

#### Extraction of routine data

**Sources:**

| Questionnaires 1–3, telephone interviews |
|-----------------------------------------|
| Study participant: name, gender, date of birth, maternity hospital, gestational age, birth weight, birth length, multiple birth, birth order, vaccinations |
| Feeding (breastfed, gastroesophageal reflux, hypoallergenic supplement), supplementary alimentation, later diet |
| Maternal and paternal hay fever, atopic dermatitis, asthma, therapy due to asthma or difficulty breathing |
| Demographic and socio-economic information: mother and father: names, birth dates, occupation throughout study, nationality, religion, country of birth and language, all home addresses from pregnancy throughout study |
| Families’ paediatrician name and address as well as of general practitioner, family history |
Questionnaire 1 contains validated questions from a preschool cohort study, including questions for school-age children from the International Study of Asthma and Allergies in Childhood (ISAAC). All questionnaires have been validated and used, with little variation since 1999. Questionnaire 1 is programmed as an online database for data entry during interview. Questionnaires 2 and 3 are distributed to parents in paper form (see available as Supplementary Data at IJE online data A and B available as Supplementary Data at IJE online).

Weekly telephone interviews (iii): these interviews are carried out during the first year of life to collect information about respiratory symptoms. This includes a standardized score with a high sensitivity for lower respiratory-tract infections (Table 4). Changes in socio-demographic and environmental exposures are also assessed (listed in Table 5 for the study population with data from Phase 1). In the event of a first lower respiratory-tract infection, the study nurses visit the families twice within 3 weeks and perform two anterior nasal swabs for virus diagnostics by polymerase chain reaction (PCR).

Objective measurements (iv): these measurements during infancy include, besides the mentioned virus diagnostics, a lung function test at the age of 1 month in unsedated infants during quiet natural sleep (tidal breathing measurements, multiple breath washouts, interrupter resistance measurements). At the age of 6 years, the same lung function tests are performed, supplemented by spirometry and bodyplethysmography. The fraction of exhaled nitric oxide (FeNO), as a marker of airway inflammation, is measured at both time-points. All measurements are performed according to current standards by the ERS and the American Thoracic Society (ATS). Skin-prick tests are performed in mothers during the first visit and in infants at the age of 6 years.

In addition to data from questionnaires, ETS exposure during pregnancy is objectively assessed by the analysis of the first urine after birth. Exposure to outdoor air pollution on the community level is measured by monitoring stations of the Swiss National Air Pollution Network (NABEL), including daily mean levels of particles with a 50% cut-off aerodynamic diameter of 10 μm (PM10) and nitrogen dioxide (NO2), as well as the daily maximum of mean hourly levels of ozone (O3). Air pollution at the individual level is measured in selected time periods by mobile passive samplers (daily mean levels of particles with a 50% cut-off aerodynamic diameter of 2.5 μm (PM2.5) and PM10) and stationary passive samplers at the measurement sites (daily mean levels of NO2).

What has been found? Key findings and publications

Development and standardization of non-invasive lung function tests
To assess lung development in a large infant cohort, one needs non-invasive tests that can be performed in uncooperative study participants. In addition to the standardized data collection, we have significantly added to current ERS/ATS standards of lung function measurements in infants and to the development and standardization of additional non-invasive lung function techniques.

Early programmers of lung development
Since the beginning of our prospective birth cohort, we have investigated physical properties of the airways in infants prone to wheeze. We showed that not only bronchoconstriction, but also impaired airway growth, plays a role for the development of wheeze. Even without current wheeze, infants with a past history of wheeze display altered airway wall mechanics. This might be due to remodelling or independent developmental differences already present at birth. This emphasizes the importance of early programmers of lung development.

Outdoor air pollution might be such an early programmer. By modelling outdoor air pollution exposure during pregnancy, we found that exposure to PM10 was associated with altered lung function in newborns and that NO2 levels were associated with elevated FeNO levels after birth, indicating the induction of inflammatory response in infants. This was enhanced if mothers smoked during pregnancy but independent of maternal atopy. Although atopy is a risk factor for allergic asthma, this adds to the hypothesis that lung development and evolution of...
Prevalence, risk factors and prognosis of respiratory symptoms in early life

We were among the first to present prospective data on respiratory symptoms in a cohort of unselected infants. The incidence of symptoms was increased in infants of asthmatic mothers, whereas maternal hay fever was inversely related to the number of symptoms. High FeNO levels after birth were associated with severe symptoms during the first year of life in the offspring of atopic mothers, which was again pronounced if mothers smoked during pregnancy. Thus, FeNO after birth might be an important predictor of later respiratory symptoms and morbidity.

The role of viral triggers for early respiratory-tract infections

We analysed the pattern of viral pathogens causing respiratory infections during the first year of life and found that rhinoviruses were most common, followed by corona, parainfluenza and respiratory syncytial viruses. Patterns differed also with regard to the amount of viral shedding 3 weeks after incidence of symptoms. Additionally, we showed that Human Bocavirus (HBoV), a picornavirus isolated in children with lower respiratory-tract infections from several retrospective and hospital-based studies, is also associated with respiratory disease in healthy Swiss infants, and reported that HBoV circulates in an endemic fashion in the community, thus confirming the worldwide distribution.

Early mechanisms and markers related to airway inflammation, the development of the immune system and childhood wheezing disorders

We were able to add towards the knowledge about the effects of environmental triggers on airway inflammation. We found that smoking during pregnancy has an effect on components of the innate immune system of the offspring. Total leucocyte counts in cord blood were significantly lower if mothers smoked during pregnancy. The decrease was most prominent in neutrophils, monocytes, dendritic cells and lymphocytes. Investigating the impact of outdoor air pollution on cytokine levels as of monocyte chemotactic protein-1 (MCP-1), interleukin-6 (IL-6), IL-10, for which large changes are seen after exposure to high pollution levels such as after bushfires, we found only small effects in cord blood of healthy term infants.

Assessing the quantitative effect of the acute-phase plasma collection mannose-binding lectin (MBL) on respiratory morbidity, we found that low levels were only weakly associated, and high levels more strongly associated, with the incidence and severity of respiratory symptoms during the first year of life, particularly in infants with asthmatic parents.

What are the main strengths and weaknesses?

The BILD cohort, with its unique data set of comprehensive lung function data, particularly during

| Table 5 Risk factors for respiratory disease of infants during Phase 1 of the BILD cohort |
|---------------------------------|---------------------------------|
| **Number** of infants | **Proportion of infants (%)** |
| **History of maternal asthma** |  |
| Negative | 320 | 88.6 |
| Positive | 39 | 10.8 |
| Unknown | 2 | 0.6 |
| **History of paternal asthma** |  |
| Negative | 323 | 89.0 |
| Positive | 36 | 9.9 |
| Unknown | 4 | 1.1 |
| **History of maternal atopic disease**<sup>a</sup> |  |
| Negative | 233 | 64.2 |
| Positive | 126 | 34.7 |
| Unknown | 4 | 1.1 |
| **Skin-pick test results in mothers**<sup>b</sup> |  |
| Negative | 197 | 65.0 |
| Positive | 106 | 35.0 |
| **Maternal smoking during pregnancy** |  |
| Negative | 316 | 87.5 |
| Positive | 42 | 11.6 |
| Unknown | 3 | 0.8 |
| **Paternal smoking during pregnancy** |  |
| Negative | 280 | 77.1 |
| Positive | 76 | 20.9 |
| Unknown | 7 | 1.9 |
| **Older siblings** |  |
| None | 181 | 50.1 |
| One | 114 | 31.6 |
| More than one | 58 | 16.1 |
| Unknown | 8 | 2.2 |

This Table shows the distribution of risk factors for respiratory disease of study participants during Phase 1 of the BILD cohort, i.e. during the first year of life (n = 364, information could not be retrieved for 3 out of 14 drop-outs during Phase 1).

<sup>a</sup>Either maternal history of allergic rhinitis, allergic asthma or atopic dermatitis.

<sup>b</sup>Skin-prick tests were performed in a subgroup of 303 mothers. Tests were positive in case of hives bigger than positive control (histamine) in any of the tested common allergens.
infancy, is an integrative and interdisciplinary framework to analyse how predisposing factors affect lung development from pregnancy through childhood and to predict later risk of respiratory disease. Especially with regard to the costly and time-consuming lung function measurements in infants, the BILD cohort has a number of methodological strengths, and normative data collected during these measurements in the BILD cohort have been published meanwhile. To ensure comparability, we measure lung function at any age in a standardized way, using the same technique and equipment on every subsequent occasion in the same order. Measurements are performed according to the latest recommendations by the ERS and ATS; often we were even stricter. For instance, according to the latest recommendations by the ERS technique and equipment on every subsequent occasion in the same order. Measurements are performed according to the latest recommendations by the ERS and ATS; often we were even stricter. For instance, according to the latest recommendations by the ERS

Can I get hold of the data? Where can I find out more?

The Bern cohort studies are carried out at the Department of Paediatric Pulmonology at Children’s University Hospital Bern, Switzerland. The department’s homepage provides information regarding personal contact data, team members and publications (http://www.kinderkliniken.insel.ch/kiihepneumologie.html). The principal investigator is Prof. Dr Urs Frey, MD PhD, head of the University Children’s Hospital (UKBB), Basel, Switzerland. Researchers interested in collaborative work or further information are invited to contact the principal investigator, Urs Frey, urs.frey@ukbb.ch.

Supplementary Data

Supplementary Data are available at IJE online.

Funding

Swiss National Science Foundation (32003B_124654/1, 3200-B0-12099, to O.F.; 3200-B0-12099, 3200-052197.97/1 to P.L.; 3200-B0-12099, 3200-052197.97/1, 3233-069348, 3200-069349 to C.K.; and 3200B_124654/1, 3200-B0-12099, 3200-052197.97/1, 3200-052197.97/2, 3200-068025 and 32-68025.02 to U.F.); European Respiratory Society (long-term research fellowship 675 to O.F.); Austrian, German and Swiss Paediatric Respiratory Society (training scholarship 2009 to O.F.).

Acknowledgements

We thank all study participants and their families in the canton of Bern for participating in the study and the staff of the four major maternity hospitals in the Bernese region (Klinik Eingeried-Sonnenhof, Lindenhofspital, Salem-Spital, Universitätsklinik für Frauenheilkunde Bern) for support and recruitment.

All involved families were recruited in maternity hospitals and only a minority of children born during the study period in the region was recruited. Although the main reason for non-participation was lacking information about the study, participants are likely to be biased towards a well-educated middle-class population. This is the case with most studies involving detailed measurements. In our analyses, social class has so far neither been a risk factor nor a risk modifier for outcome measures. Therefore, although we believe that most results are fairly representative for the general population, it must be kept in mind that not all findings can be extrapolated to all Swiss or European children. Replication of the findings in independent cohorts is desirable.
We also thank the study nurses Monika Graf, Barbara Hofer and Christine Becher and the lung function technicians Gisela Wirz and Sandra Luescher for their invaluable assistance and support.

Conflict of interest: None declared.

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