

ORIGINAL ARTICLE

Can childhood asthma be predicted at birth?

K. C. Lødrup Carlsen^{1,2}, P. Mowinckel¹, B. Granum³ and K.-H. Carlsen^{2,4}¹Department of Paediatrics, Oslo University Hospital, Ullevål, Norway, ²Faculty of Medicine, the University of Oslo, Oslo, Norway, ³Division of Environmental Medicine, Norwegian Institute of Public Health, Norway and ⁴Department of Paediatrics, Oslo University Hospital, Rikshospitalet, Oslo, NorwayClinical &
Experimental
Allergy

Summary

Background Early life appears optimal for prevention of asthma, but interventions require a relevant target population, to date not clearly identified at birth.**Objective** We therefore aimed to identify the predicting capacity of factors known around birth for asthma and rhinitis at 10 years.**Methods** The included 614 healthy term babies with lung function measured at birth in the 1992/1993 Environment and Childhood Asthma study in Oslo attended a 10-year follow-up visit including a structured interview and skin prick test (SPT) for allergies. The logistic regression analyses included 37 general variables from an extensive birth questionnaire; lung function; cord blood total immunoglobulin E and soluble CD14. A history of asthma, current asthma, history of rhinitis and 'healthy' (no history of asthma, rhinitis and negative SPT) was predicted on a group level and individual predicted probabilities were calculated.**Results** The predictability of the models [area under the curve (95% confidence intervals)] was 0.74 (0.69, 0.79), 0.72 (0.64, 0.78), 0.69 (0.54, 0.72) and 0.67 (0.62, 0.71) for a history of asthma, current asthma, rhinitis and 'healthy', respectively. The best model predicted a history of asthma correctly in 93/124 (75%), and incorrectly in 176/490 (36%) children without asthma. The positive predictive values for all outcomes were low (19–61), the highest predicting healthy.**Conclusion** Although at best 75% of children with a history of asthma could be predicted at birth, an intervention applied to our predicted high-risk children would be started more often in children without than with future disease. Parental allergic disease alone appears insufficient to identify high-risk populations in future studies of asthma and allergic disease.**Keywords** asthma, birth, child, predict, rhinitis*Submitted 15 March 2010; revised 6 July 2010; accepted 9 August 2010.*

Correspondence:

Karin C. Lødrup Carlsen, Department of Paediatrics, Oslo University Hospital, Ullevål and the Faculty of Medicine, University of Oslo, NO-0407 Oslo, Norway.

E-mail: k.c.l.carlsen@medisin.uio.no

Introduction

Identification of risk factors for disease, presently asthma, is important for understanding mechanisms of disease development, implement possible preventive strategies [1] and institute early appropriate management in children at risk. However, risk factor identification is usually insufficient to screen for, or to predict disease in individual subjects [2–4].

Although risk factors for asthma have been identified in a number of well-conducted birth cohort and other studies [5–9], the ability of many risk factors observed at birth to predict asthma or other obstructive airways disease outcomes in childhood is largely unknown. On the other hand, early disease manifestations in young children can

to some [10–12] or larger [13, 14] extent predict asthma in later childhood, whereas assessing predictability of early life factors for adult asthma [15, 16] remains difficult [15].

Among identified perinatal risk factors for childhood asthma are: parental atopy (particularly asthma, but also asthma and/or allergic rhinitis) [9, 17], male gender [10, 18], maternal smoking also during pregnancy [19, 20], reduced lung function [20], increased cord blood immunoglobulin E (IgE) [21, 22], large head circumference [7], low birth weight and perinatal complications [23]. With the recent western world asthma epidemic, the asthma increase appears to occur mainly among children without known genetic predisposition [4, 24], suggesting a dominating environmental influence. Thus, although parental allergic disease roughly doubles the risk of asthma [9], it

appears less important as a predictor for asthma in the offspring [4, 18].

Birth cohort studies designed to assess asthma development have the potential of predicting asthma and often include information at various time-points on constitutional, socio-economic, pregnancy-related, environmental and to some extent genetic risk factors. However, few [25] include lung function shortly after birth, which has been shown to be associated with asthma in school age children [26]. These variables may be helpful to facilitate an understanding of *which* factors are implicated in asthma development, *when* they may exert their effects and the *individual and summated effect* of these risk factors at certain time-points in life. However, these have rarely been assessed in true prediction models for later disease in individual subjects. To our knowledge, none have attempted predicting asthma-related outcomes in later childhood by factors known at the time of birth, a point of importance for identifying children at risk for possible primary intervention studies [27].

The aim of the present study was to assess if it is possible to predict asthma or rhinitis at 10 years by factors known *at the time of birth* (including lung function measured in the first 5 days of life).

Subjects and methods

Study design

The present study concerns 616/802 (77%) children enrolled at birth with lung function measured at a mean of 2.7 days who attended a 10-year follow-up study of the 1992–1993 birth cohort ECA study in Oslo [18]. This cohort represents a general urban population sample of children who were healthy at birth, had at least 2000 g birth weight and at least 36 weeks gestational age, no requirement for supplementary oxygen or ventilatory support by 6 h of life and parents with sufficient language skills to complete questionnaires [25]. Before leaving the maternity ward, parents completed a questionnaire, and the midwives recorded the babies' health information in a registry card. Owing to restricted resources for further follow-up studies, after 2 years we chose to invite all children with lung function measured at birth (a general cohort with the exception that they all had vaginal deliveries) as well as all children in a nested case-control study at 2 years (described elsewhere) [18]. The present study, however, included only children from the general population sample; i.e. all children with lung function measured at birth. At 10 years the children attended a 2-day investigation including clinical evaluation, measures of lung function and bronchial hyperresponsiveness (exercise and methacholine challenge tests) and allergological investigations [18, 26].

Written informed consent was obtained from parents of all subjects. All parts of the study were approved by the Regional Committee for Medical Ethics, the Norwegian Data Inspectorate and registered in the Norwegian Biobank Registry.

Subjects

The children attending the 10-year follow-up study were comparable at birth with those who did not, with respect to lung function [26] as well as to the remaining 3140 cohort children, with the exception of slightly lower birth length, head circumference and lower ponderal index (Table 1).

A history of asthma and a history of rhinitis were determined among 614/616 children (331 boys, 283 girls) (mean age 10.9 ± 0.8 years). Current asthma was defined in 67/607 (11.1%) (seven asthma children had incomplete data for classification of current disease) [18]. Variables to determine 'Healthy' were available in 605 children. Children with current asthma as well as a history of asthma had significantly reduced baseline lung function [forced expiratory volume at 1 s (FEV_1) and forced expiratory flow at 50% expired volume (FEF_{50})] at 10 years compared with subjects without a history of asthma [18, 26].

Methods

At birth. The questionnaire completed by the parents included factors given in Fig. 1. Parental smoking during pregnancy was asked as none, sporadic or daily smoking [20, 28] and complications during pregnancy (Fig. 1) were mostly recorded as yes/no. All questions on parental variables were recorded separately for mother and father, except for parental total income.

Lung function was measured using a facemask in awake, quietly breathing infants [25] with the Sensormedics 2600 System (SensorMedics Corp., Anaheim, CA, USA). For details, see supporting information. Cut-off levels of lung function were chosen on the basis of previous studies as $>$ vs. $\leq$ median with the addition of $t_{PTEF}/t_E < 0.20$ [25].

Cord blood soluble CD14 and total immunoglobulin E. See supporting information for details of analyses.

At 10 years

Parental structured interviews. Parents responded to a detailed, physician-conducted structured interview with questions of respiratory symptoms and asthma management [18].

Lung function and exercise challenge test were performed according to international guidelines as described

Table 1. Demographic information of the 614 children examined at birth as well as at 10 years, the 188 children lost to follow-up from birth to 10 years as well as the remaining cohort ($n = 3140$) not eligible for inclusion in the present study

At birth	Included $N = 614$	Lost to follow-up $N = 188$	Not included $N = 3140$	<i>P</i> -value included vs.	
				Lost to follow-up	Not included
Gender (boys %)	284 (46.1)	83 (48.0)	1487 (48.3)	0.66	0.33
Gestational age (weeks (SD))	39.6 (1.0)	39.7 (0.9)	39.8 (1.1)	0.31	0.02
Birth weight (grams (SD))	3549 (514)	3516 (486)	3591 (488)	0.07	0.06
Birth length (cm (SD))	50.4 (3.6)	50.1 (2.4)	49.7 (2.7)	0.22	<0.0001
Head circumference cm (SD)	35.8 (1.5)	35.8 (1.4)	35.3 (1.6)	0.99	<0.0001
Ponderal index*	2.85 (0.70)	2.81 (0.47)	3.00 (1.04)	0.52	0.0001
Older siblings yes, (n (%))	272 (44.3)	74 (39.3)	1331 (42.2)	0.71	0.25
Parental asthma (n (%))	74 (12.0)	22 (12.3)	382 (12.0)	0.92	0.91
Parental hayfever (n (%))	183 (29.7)	49 (27.4)	853 (27.2)	0.55	0.20
Parental eczema (n (%))	193 (31.3)	46 (25.7)	877 (28.0)	0.15	0.09
Parental education†	5 (1, 7)	5 (1, 7)	5 (1, 7)	0.07	0.07
Alcohol in pregnancy (n (%))	367 (59.6)	95 (53.4)	1863 (59.5)	0.14	0.96
Cat at home	45 (7.3%)	10 (5.6%)	237 (9.2%)	0.43	0.83
Dog at home	56 (9.1%)	9 (5.0%)	288 (9.2%)	0.08	0.94

Alcohol in pregnancy: yes or no by maternal use during pregnancy.

*Ponderal index: birth weight (g) $\times$ 100/birth length (cm)³.

†Parental education given (median, min–max) category from 1 (lowest) to 6 highest (university).

The following 54 variables (answered at birth) were included in the final general domain :

- Gender
- Birth weight
- Birth length
- Ponderal index
- Head circumference
- Apgar score
- Calendar week of birth
- Birth year of mother,
- Birth year of father
- Parents cohabitate
- Siblings (yes/no)
- Have cat
- Have dog
- Parental* smoking (yes/no)
- Smoking by others in household (yes/no)
- Maternal use of alcohol during pregnancy
- Pregnancy
- Use of medication
- Sick leave certified by a MD
- Exercise in the first, second and third trimester
- Normal pregnancy (yes/no)
- If no; haemorrhage
- Reduced fetal growth
- Hypertension
- Hyperemesis gravidarum
- Threatening premature labour
- Preeclampsia
- Other pregnancy-related complaints
- Parental* asthma
- Parental* atopic eczema
- Parental* hayfever
- Parental* diabetes
- Parental* cancer
- Parental* epilepsy
- Parental* heart disease
- Parental* education
- Parental total gross income
- Standard of house/flat
- Proximity to traffic
- Concern for outdoor pollution
- Sources of air pollution near Home (other than traffic)
- How simple to get a baby-sitter In the evening,
- How simple to get a baby-sitter for errands (daytime)
- Network of relatives
- Economic stress

Fig. 1. The 54 variables included in the general domain, all *parental outcomes were initially entered separately (maternal and paternal), but eventually included as parental (none vs. at least one) except for gross parental income (total). Economic stress was answered by 'how easy would it be to pay an unexpected bill of 5000 NOK (in 1992/1993)' (see supporting information for details).

previously [18] with a positive exercise test defined as a fall in $FEV_1 \geq 10\%$ 3–20 min after running.

Methacholine challenge test was performed by international standard methods [29] and is given by the dose of methacholine required to cause a fall in FEV_1 of 20% of post saline values (PD_{20}).

Skin prick test. Skin prick tests (SPT) to common inhalant and food allergens were performed in 608 children [18] with

Soluprick[®] allergens (ALK Albello, Hørsholm, Denmark). Sensitization was considered positive with a mean diameter ≥ 3 mm larger than the negative control (saline) for at least one allergen (given in the supporting information).

Definitions and outcomes at 10 years. A history of asthma was defined in children by the presence of at least two of the three criteria; asthma symptoms, doctor diagnosis of asthma and/or use of asthma medication [26].

Current asthma was established in a child with a history of asthma with symptoms, use of asthma medication within the last 12 months and/or a positive exercise challenge test at the 10 year follow-up visit [18].

A *history of rhinitis* was present in children reporting at least one major and one (other) minor criterion of rhinitis symptoms, treatment for rhinitis symptoms and/or a doctor diagnosis of rhinitis (see supporting information for details).

Healthy in this context refers to children reported with no history of asthma or rhinitis and with a negative SPT at 10 years.

Exposure and explanatory variables at or around birth.

Predictors were grouped in three domains [1–3] and one risk group was [4] identified in previous analysis [26]:

1. General domain: 54 variables identified as possibly relevant information from questionnaires and registry cards (Fig. 1).
2. Cord blood variables: sCD14 and total IgE.
3. Lung function at birth: t_{PTEF}/t_E , V_E , Crs and Rrs.
4. Risk group: crs < median and $t_{PTEF}/t_E < 0.2$.

Statistical analyses

Results are given as odds ratios (OR) with 95% confidence intervals (CI) when appropriate.

Size at birth was given as birth weight and length as well as by a ponderal index (birth weight (g) × 100/birth length (cm)³) [30]. Further details on variables entered into the analyses are given in the supporting information.

Multivariate logistic regression analysis was performed separately for each of the four outcomes in a step-down procedure to select covariates as suggested by Hosmer and Lemeshow [31]. Variables with a *P*-value < 0.25 were kept in the models. In the step-down procedure, variables taken out of the analysis were tested for confounding. Predictors were entered stepwise in the four domains and subsequently the risk group was added to the analyses.

Interactions were considered and tested in each model. Using the best-fit logistic regression models for each outcome, predicted probabilities were calculated by using the natural logarithm of the ORs for each individual, including the outcome prevalence (Table 3) from our cohort (supporting information, Table S2). The estimated probabilities were included in a receiver operating characteristics (ROC) analysis to establish whether we could identify a well-functioning diagnostic rule. For the optimal cut-off value, the sensitivity, specificity, positive and negative predictive values with 95% CI were calculated.

To demonstrate the appropriateness of the prediction model, the number of children with correct and incorrect

prediction is given (Table 3), as well as the ROC curves for each model (supporting information, Fig. S1).

The analyses were performed with Statistical Analysis System and R (see supporting information for details).

Results

Significant prediction models were identified for all outcomes, with significant variables found in all domains (Table 2) except cord blood (IgE and sCD14), which is subsequently not further reported. The best model explained the outcome variation (r^2) by the included variables for a history of asthma of 17.5% followed by 'healthy' (10.8%), current asthma (10.4%) and a history of rhinitis (9.9%) (reported for each domain in supporting information, Table S1).

The predictive ability of the models given by the area under the curve [AUC (95%CI)] identified the best prediction model for a history of asthma 0.74 (0.69, 0.79) followed by current asthma 0.72 (0.64, 0.78), rhinitis 0.69 (0.54, 0.72) and healthy 0.67 (0.62, 0.71), respectively (supporting information, Fig. S1).

The optimal models (supporting information, Table S2) were used to estimate a predicted probability for each individual for the four outcomes. The identified optimal cut-off levels with sensitivity, specificity, positive and negative predictive values for prediction as well as the number and percent children who by the models were correctly predicted with or without the respective outcomes are given in Table 3.

The best model predicted correctly (Fig. 2) 93/124 (75%) with a history of asthma, and 43/67 (64%) with current asthma, but inappropriately predicted the same outcome (in children without a history of or current asthma) in 176/490 (36%) and 178/540 (33%) children, respectively (Fig. 2). Being 'healthy' (no history of asthma or rhinitis and no allergic sensitization at 10 years) was correctly predicted in 214/306 (70%) children, and thus 92 children who were in fact healthy were not identified with the optimal model. Likewise among the 299 children with asthma and/or a history of rhinitis, 132 children (44%) were predicted to be healthy.

The optimal models demonstrated that the general domain contained significant variables for all outcomes, largely due to the observed gender effect (Table 2), which was the only risk factor that was significant for all outcomes. Alcohol use in pregnancy was associated with a reduced risk of both asthma outcomes; parental rhinoconjunctivitis increased the risk of a history of asthma and a history of rhinitis whereas economic stress was associated with a history of rhinitis (Table 2).

Significant interaction was observed between gender, and economic stress (for detailed OR and 95% CI see supporting information, Table S3). After stratification for gender, a significant effect by economic stress was found

Table 2. Significant birth and perinatal predictors given with odds ratios (95% CI) in the best models for predicting current asthma, a history of asthma, a history of rhinitis or healthy (never wheeze, no history of rhinitis and no positive skin prick tests at 10 years)

Domain (reference)	Current asthma	History of asthma	Rhinitis ever	Healthy
General				
Gender (girl)	2.31 (1.31, 4.07)	1.05 (0.77, 1.43)	1.85 (1.27, 2.70)	0.46 (0.32, 0.64)
Babysitter day time (1–10)	1.07 (1.00, 1.13)			
Family network (1–10)	0.79 (0.65, 0.96)	0.86 (0.75, 0.98)		
Alcohol in pregnancy (no)	0.57 (0.33, 0.97)	0.53 (0.33, 0.86)		1.61 (1.15, 2.25)
Economic stress (1–10)			1.06 (1.01, 1.12)	0.95 (0.91, 0.98)
Parental rhinoconjunctivitis (no)		1.88 (1.06, 3.34)	1.49 (1.14, 1.94)	
Parental education (1–6)		0.74 (0.59, 0.91)		
Cohabitation (no)			0.27 (0.07, 0.95)	
Having siblings (no)			0.45 (0.30, 0.68)	
Lung function				
Resistance ($\leq$ median)		0.60 (0.36, 0.97)		
Ve ($\leq$ median)	2.24 (1.29, 3.89)	2.48 (1.49, 4.12)		0.60 (0.43, 0.83)
t_{PTEF}/t_E (≤ 0.20)		1.38 (1.01, 1.89)		
Interactions				
Gender (girl)* t_{PTEF}/t_E (≤ 0.20)		2.72 (1.32, 5.61)		
Gender (girl)* Economic stress (1–10)			0.94 (0.90, 0.99)	

Baby sitter: how easy is it to get a babysitter during day time for an errand?; Family network: How easy will it be to contact family or friends for questions related to care of the baby?; Economic stress: how easy will it be to pay an unexpected bill in 1992/1993 of 5000 NOK? All three variables given on a visual analogue scale from 1 to 10 (1 being very easy and 10 impossible); Parental education given for parent with the highest education: 1–6 (1 being 9–10 year at school and six University education); Alcohol: maternal use of alcohol in pregnancy; Cohabitation: parental cohabitation.

*Significant interactions were observed for the following models that are given in details in the online supplement.

Table 3. The predictive capacity on an individual level given for the best prediction models at birth for 10-year outcomes in the environment and childhood asthma general birth cohort study

Outcome n/total (prevalence)	Prediction value	Sensitivity	Specificity	PPV	NPV
Current asthma $n = 67/607$ (11.0)	0.12	64 (54, 73)	67 (63, 70)	19 (15, 24)	94 (91, 95)
History of asthma $n = 124/614$ (20.2)	0.20	75 (67, 81)	64 (60, 68)	35 (30, 41)	91 (87, 93)
History of rhinitis $n = 116/614$ (18.9)	0.26	73 (63, 81)	50 (45, 55)	29 (23, 35)	87 (82, 91)
'Healthy'* $n = 306/605$ (50.6)	0.47	70 (65, 75)	56 (50–61)	61 (56, 65)	65 (60, 71)

The predictive capacity for the model is given for each outcome with corresponding sensitivity, specificity, positive and negative predicted values and their respective 95% confidence intervals in parenthesis for the optimal cut-off value (value) identified with a receiver operating curve (ROC) (see Fig. S1).

*Healthy: no history of asthma or rhinitis and no positive skin prick tests at 10 years.

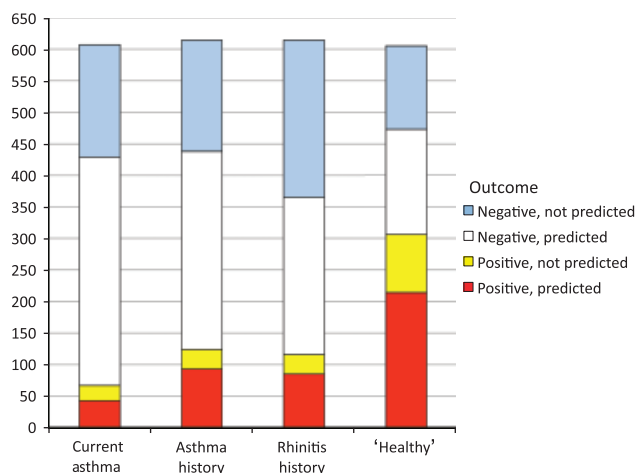


Fig. 2. The appropriateness of the best prediction models given by number of children in the general birth cohort classified (predicted) correctly or incorrectly at birth according to 10-year outcomes.

among girls only, but with an r^2 of only 6%. Thus, the non-stratified model is given.

The only other interaction found was between gender and $t_{PEF}/t_E \leq 0.20$ for the outcome of a history of asthma (supporting information, Table S1). However, by stratification of gender the prediction capacity of the model decreased, whereas the risk effects did not change considerably. The presented model consequently includes all children.

Discussion

The present study demonstrated for the first time that at best the models could correctly predict 75% of children with a history of asthma, whereas the included birth characteristics explained 17.5% of the outcome variability at 10 years of age. Although the predictability of the models were reasonable with an AUC of 67–74%, more children were wrongly than correctly classified with asthma by 10 years and the positive predictive values of the models were low. Without lung function measurements, < 10% of the variation could be predicted in any outcome.

The present study is to our knowledge the first to determine systematically on group as well as individual levels what variables around birth may predict asthma and rhinitis 10 years later. A prediction model is considered good with an AUC of at least 80%, suggesting only a moderately good predictive ability of the present birth prediction models. These are however in line with a reported AUC of 66–68 for a prediction models in a similarly sized study ($n = 693$) of Dutch children followed from 2 to 21 years [16] identifying childhood factors at 2 and 4 years, respectively, to predict asthma in young

adulthood. Their final models included female gender, smoking mother, lower respiratory tract illness and atopic parents and they concluded that satisfactory prediction of asthma in young adults could not be performed based upon childhood characteristics. On the other hand, risk scores are reported for school age wheeze based upon childhood characteristics during the first 3 years of life for later asthma-related outcomes [14, 32], a pre-school score for children followed for 1 year [11], as well as the Oslo score at 2 years for ongoing asthma at 10 years [13]. The predictive capacities however were considerably better for childhood [13, 14] than adult outcomes [16].

Depending upon the aims of prediction, there are at least two ways to interpret the results of the present study. First, for a history of asthma and current asthma at best only 17.5% and 10.4% of the variability of the outcomes, respectively were identified implying that the majority of factors determining asthma in childhood were not detected at birth. Without including lung function measurements, which are rarely available, the explained variability was < 10%. In fact, we also added the common beta2-receptor genotypes to the models, but these were not significantly associated with the outcomes, nor did they improve predictability (data not shown). Thus, many potentially adverse factors acting only after birth may play a role in asthma and rhinitis development. On the other hand, identifying subjects appropriate for intervention programs [27] by our prediction models at birth would lead to interventions in more children without ($n = 176$) (white bars in Fig. 2) than with ($n = 93$) (red bars, Fig. 2) a future history of asthma, and fail to intervene in a number of children ($n = 31$) (yellow bars, Fig. 2) who would develop a history of asthma (Table 3). Such considerations are important in planning possible primary prevention strategies [11, 27].

Sly et al. [27] highlighted recently the importance of early identification of children at risk of asthma, and the present study extends the current knowledge of how to do so. Thus, we aimed to determine the extent to which it is possible to predict asthma related outcomes by factors known at birth. Consequently, possible interactions with or influences of later exposures were not included in the present analyses.

The identified risk factors are mostly in line with previous reports. Boys are at risk of asthma phenotypes before puberty, [10, 27] whereas parental rhinoconjunctivitis is often reported for asthma [33] and rhinitis [24]. Maternal alcohol use during pregnancy was only reported as a dichotomous variable, but was associated with a reduced risk of all asthma-related outcomes. To our knowledge, *in utero* exposure to alcohol has been associated with an increased IgE [34] and childhood atopic eczema [35] but not with childhood asthma [36]. The explanation for our finding is unclear. It is uncertain whether the observed protective effect of *in utero* alcohol

exposure for asthma is a direct effect or a marker of some life style or other factor that we are unable to detect or that the inclusion criteria (healthy newborn babies) may favour this association. Inability to pay an unexpected bill may be a marker of family stress that has been implicated in asthma development [37]. The present study has not sufficient information to suggest further biological plausible explanations for these associations, but the observation warrants further studies addressing this important issue. Atopy in one parent, often used as inclusion criteria into high-risk cohorts [11, 38] did not appear appropriate to target children with ongoing asthma at 10 years.

The lack of significant prediction by maternal smoking *in utero* and pregnancy-related complications are in line with the suggested diminishing effects of risk factors with an increasing age [19, 32]. The present analyses included most other factors reported or suggested to be associated with asthma, possibly reducing the potential association identified by singular factors. Furthermore, the present cohort included healthy babies, reducing the likelihood of identifying severe pregnancy complications as significant predictors.

Few interactions were detected in the present study (Table 2 and supporting information, Table S1), both involving gender. However, by gender stratification the prediction capacity decreased without significant alteration of risk effects, and thus we chose to present the models including all children.

Both asthma outcomes (a history of asthma and current asthma) may represent heterogeneous phenotypes [32], but were nevertheless associated with significantly reduced baseline lung function at 10 years. They are therefore likely to represent a reasonable classification of asthma subjects. A positive exercise test was chosen to classify current asthmatics as this may represent ongoing asthma in childhood, even in children not experiencing symptoms [18]. Wheeze without other asthma-related symptoms was not included in our asthma outcomes, as we suggest that these children are unlikely to have asthma as sought in the present context. To further specify asthma phenotypes, we tested for the prediction of current asthma with a positive metacholine challenge (defined by $\leq 8 \mu\text{mol}$ metacholine) as well as current asthma with allergic sensitization (a positive SPT and/or specific IgE to common allergens $> 0.35 \text{ kU/L}$) without being able to identify significant models (data not shown). This may be a result of reduced number of children with positive outcomes. Although rhinitis was based upon a history of symptoms and/or medication, 82.5 per cent were sensitized to at least one allergen (data not shown), supporting predominantly allergic rhinitis [39].

The present study is strengthened by the prospective study design of a general population with well-characterized children including lung function measurements at birth and at 10 years [26] as well as the relatively high

follow-up rate (77%). The methods used are standard for developing prediction models, with few missing data (data not shown). All variables were tested for confounding and the final main effect model was tested for significant interactions. Furthermore, over-fitting was not found in our resultant models, as demonstrated in further analyses with Aikake information criterion in $R^{\text{®}}$ (data not shown). The present final main effects models were similar to the criterion-based model with similar results; with one exception; For 'History of asthma', the additional variable 'How easy it is to pay an unexpected bill' was included in the criterion-based model. Furthermore, to ascertain that important information was not missed using dichotomized compared with continuous variables, we also performed a multivariable fractional polynomial regression using fractional polynomials of continuous covariates: parsimonious parametric modelling. This identified no functional form (not even linear) for the lung function variables suggesting that dichotomized lung function values were appropriate. Reanalyses of predictive capacity of a few, and simple risk factors (parental asthma/rhinitis, maternal smoking, gender and maternal age) demonstrated poorer results, with at least 5% better predictability by the reported models (data not shown).

Cord blood analyses were not predictive of asthma outcomes 10 years later, and insufficient power is unlikely to explain this finding [40]. We could not quantify alcohol consumption during pregnancy, and inclusion of healthy newborn babies precluded inclusion of serious pregnancy-related complications in the analyses. The general application of our results including lung function measurements is limited because such measurements are not commonly available. However, the main result remains generally valid; that correct prediction at birth of asthma or allergic rhinitis later in life is difficult.

Conclusion

Despite well-known risk factors, childhood asthma is difficult to predict at birth. Although the majority of children with asthma were correctly predicted, a high number of children were incorrectly predicted both with and without disease. Incorrect prediction may have implications for the results of intervention trials in high-risk children, and parental atopy alone is probably insufficient to identify a high-risk population in future studies of asthma and allergic disease.

Acknowledgements

We are indebted to all participants in the study and grateful to the research team involved in the clinical investigations of the follow-up study, especially to Geir Håland, Monica Cheng-Munthe Kaas, Chandra Devluapalli, Martinus Løvik, Randi Jacobsen, Morten Pettersen,

Solveig Knutsen, Trine Stensrud, Ingebjørg Coward and Anne Cathrine Mork Wik.

Sponsors for the ECA-study was initially the Norwegian Research Council, and later the University of Oslo, the Norwegian Foundation for Health and Rehabilitation, Regional Health East Authority, the Norwegian Association of Asthma and Allergy, the Kloster foundation, AstraZeneca, Pharmacia and the Hakon group.

Authors contribution:

Karin C. Lødrup Carlsen: responsible for the ECA-project 10-year follow-up, clinical PI for the initiation and first phase (1992–1995) of the ECA study, developed the hypothesis, took part in analyses of data and is responsible for writing manuscript.

Petter Mowinckel: responsible statistician, took part in developing hypothesis, performed all analyses, significant contribution to structure and writing of the paper. Has seen and approved the final version submitted.

Berit Granum: performed all s-CD14 analyses, took part in hypothesis development, significant contribution to structure and writing of the paper. Has seen and approved the final version submitted.

Kai-Håkon Carlsen: responsible for the ECA-project 10 initiation, in steering committee and part-responsible for the entire ECA-study, took part in development of hypothesis, analyses of data, writing and approving submitted manuscript.

Authors conflict of interest:

All authors; Karin C. Lødrup Carlsen, Petter Mowinckel, Berit Granum and Kai-Håkon Carlsen declare *no conflict of interest* with any sponsoring or other body for the present paper.

All have seen and approved the present version of the manuscript.

The study is performed within the ORAACLE (the Oslo Research Group of Asthma and Allergy in Childhood; the Lung and Environment), a member of the GA²LEN (Global Allergy and Asthma European Network).

References

- Arshad SH. Primary prevention of asthma and allergy. *J Allergy Clin Immunol* 2005; **116**:3–14.
- Ware JH. The limitations of risk factors as prognostic tools. *N Engl J Med* 2006; **355**:2615–7.
- Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? *BMJ* 1999; **319**:1562–5.
- Bergmann R, Woodcock A. Whole population or high-risk group? Childhood asthma. *Eur Respir J Suppl* 1998; **27**:9s–12s.
- Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson children's respiratory study: 1980 to present. *J Allergy Clin Immunol* 2003; **111**:661–75.
- Kjellman NI. IgE in neonates is not suitable for general allergy risk screening. *Pediatr Allergy Immunol* 1994; **5**:1–4.
- Fergusson DM, Crane J, Beasley R, Horwood LJ. Perinatal factors and atopic disease in childhood. *Clin Exp Allergy* 1997; **27**:1394–401.
- Bergmann RL, Edenharter G, Bergmann KE et al. Atopic dermatitis in early infancy predicts allergic airway disease at 5 years. *Clin Exp Allergy* 1998; **28**:965–70.
- Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest* 2005; **127**:502–8.
- Anderson HR, Bland JM, Peckham CS. Risk factors for asthma up to 16 years of age. Evidence from a national cohort study. *Chest* 1987; **91** (6 Suppl):127S–30S.
- Clough JB, Keeping KA, Edwards LC, Freeman WM, Warner JA, Warner JO. Can we predict which wheezy infants will continue to wheeze? *Am J Respir Crit Care Med* 1999; **160** (5 Pt 1):1473–80.
- Bahceciler NN, Barlan IB, Nuhoglu Y, Basaran MM. Risk factors for the persistence of respiratory symptoms in childhood asthma. *Ann Allergy Asthma Immunol* 2001; **86**:449–55.
- Devulapalli CS, Carlsen KC, Haland G et al. Severity of obstructive airways disease by two years predicts asthma at 10 years of age. *Thorax* 2008; **63**:8–13.
- Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000; **162** (4 Pt 1):1403–6.
- Rhodes HL, Sporik R, Thomas P, Holgate ST, Cogswell JJ. Early life risk factors for adult asthma: a birth cohort study of subjects at risk. *J Allergy Clin Immunol* 2001; **108**:720–5.
- Balemans WA, van der Ent CK, Schilder AG, Sanders EA, Zielhuis GA, Rovers MM. Prediction of asthma in young adults using childhood characteristics: development of a prediction rule. *J Clin Epidemiol* 2006; **59**:1207–12.
- Sears MR, Holdaway MD, Flannery EM, Herbison GP, Silva PA. Parental and neonatal risk factors for atopy, airway hyperresponsiveness, and asthma. *Arch Dis Child* 1996; **75**:392–8.
- Lodrup Carlsen KC, Haland G, Devulapalli CS et al. Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study. *Allergy* 2006; **61**:454–60.
- Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 1998; **53**:204–12.
- Lodrup Carlsen KC, Carlsen KH, Nafstad P, Bakkevig L. Perinatal risk factors for recurrent wheeze in early life. *Pediatr Allergy Immunol* 1999; **10**:89–95.
- Hansen LG, Halken S, Host A, Møller K, Østerballe O. Prediction of allergy from family history and cord blood IgE levels. A follow-up at the age of 5 years. Cord blood IgE. IV. *Pediatr Allergy Immunol* 1993; **4**:34–40.
- Sadeghnejad A, Karmaus W, Davis S, Kurukulaaratchy RJ, Matthews S, Arshad SH. Raised cord serum immunoglobulin E increases the risk of allergic sensitisation at ages 4 and 10 and asthma at age 10. *Thorax* 2004; **59**:936–42.
- Annesi-Maesano I, Moreau D, Strachan D. In utero and perinatal complications preceding asthma. *Allergy* 2001; **56**:491–7.
- Christie GL, McDougall CM, Helms PJ. Is the increase in asthma prevalence occurring in children without a family history of atopy? *Scott Med J* 1998; **43**:180–2.
- Lodrup Carlsen KC, Magnus P, Carlsen KH. Lung function by tidal breathing in awake healthy newborn infants. *Eur Respir J* 1994; **7**:1660–8.

- 26 Haland G, Carlsen KC, Sandvik L *et al*. Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med* 2006; **355**:1682–9.
- 27 Sly PD, Boner AL, Bjorksten B *et al*. Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008; **372**:1100–6.
- 28 Lodrup Carlsen KC, Jaakkola JJ, Nafstad P, Carlsen KH. In utero exposure to cigarette smoking influences lung function at birth. *Eur Respir J* 1997; **10**:1774–9.
- 29 Crapo RO, Casaburi R, Coates AL *et al*. Guidelines for methacholine and exercise challenge testing–1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000; **161**:309–29.
- 30 Xu B, Pekkanen J, Laitinen J, Jarvelin MR. Body build from birth to adulthood and risk of asthma. *Eur J Public Health* 2002; **12**:166–70.
- 31 Hosmer DW, Lemeshow S. *Applied Logistic Regression*, 2nd Ed. New York: John Wiley and Sons, 2000.
- 32 Matricardi PM, Illi S, Gruber C *et al*. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. *Eur Respir J* 2008; **32**:585–92.
- 33 Bjerg A, Hedman L, Perzanowski MS, Platts-Mills T, Lundback B, Ronmark E. Family history of asthma and atopy: in-depth analyses of the impact on asthma and wheeze in 7- to 8-year-old children. *Pediatrics* 2007; **120**:741–8.
- 34 Friedrich N, Husemoen LL, Petersmann A, Nauck M, Volzke H, Linneberg A. The association between alcohol consumption and biomarkers of alcohol exposure with total serum immunoglobulin E levels. *Alcohol Clin Exp Res* 2008; **32**:983–90.
- 35 Linneberg A, Petersen J, Gronbaek M, Benn CS. Alcohol during pregnancy and atopic dermatitis in the offspring. *Clin Exp Allergy* 2004; **34**:1678–83.
- 36 Yuan W, Sorensen HT, Basso O, Olsen J. Prenatal maternal alcohol consumption and hospitalization with asthma in childhood: a population-based follow-up study. *Alcohol Clin Exp Res* 2004; **28**:765–8.
- 37 Milam J, McConnell R, Yao L, Berhane K, Jerrett M, Richardson J. Parental stress and childhood wheeze in a prospective cohort study. *J Asthma* 2008; **45**:319–23.
- 38 Lau S, Nickel R, Niggemann B *et al*. The development of childhood asthma: lessons from the German multicentre allergy study (MAS). *Paediatr Respir Rev* 2002; **3**:265–72.
- 39 Bertelsen R, Carlsen K, Carlsen K. Rhinitis in children: comorbidities and phenotypes. *Pediatr Allergy Immunol* 2010; **21**:612–22.
- 40 Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The group health medical associates. *N Engl J Med* 1995; **332**:133–8.

Supporting Information

Additional supporting information may be found in the online version of this article:

Fig. S1. Receiver operating curve (ROC) analyses describing the fit of the best model to predict the four outcomes at 10 years; a history of asthma, current asthma, a history of rhinitis and ‘healthy’ (never wheeze, no history of rhinitis and no positive skin prick tests at 10 years).

Table S1. Explained variation (Nagelkerke, $r^2 \times 100$) of the outcomes by each model given by entered variable domains at or shortly after birth to predict current asthma, a history of asthma, allergic rhinitis or no history of obstructive lower airways disease or rhinitis (healthy) among 10 year old children.

Table S2. Individual predicted probability (h) models calculated from the optimal regression analysis for each outcome are given in Table 2. The model includes the natural logarithm of the OR for each variable.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

RESULTS:

Supplement table 1

Explained variation (Nagelkerke, $r^2 \times 100$) of the outcomes by each model given by entered variable domains at or shortly after birth to predict current asthma, a history of asthma, allergic rhinitis or no history of obstructive lower airways disease or rhinitis (healthy) among 10 year old children.

	Current asthma	History of asthma	History of Rhinitis	Healthy
General domain	7.7	9.2	9.9	8.0
+ CB	ns	ns	ns	ns
+Lung function	10.4	17.5*	ns	9.1
		Boys 10.0		
		Girls 14.6		
+ risk group	7.9	17.3	ns	10.8
<i>Best fit model</i>	<i>10.4</i>	<i>17.5</i>	<i>9.9</i>	<i>10.8</i>

Ns: no significant effect of domain or change in model by adding domain.

*A significant interaction was found for lung function and gender, thus Nagelkerke is given for overall prediction as well as stratified by gender.

Supplement table 2.

Individual predicted probability (h) models calculated from the optimal regression analysis for each outcome are given in table 2. The model includes the natural logarithm of the odds ratio for each variable.

Outcome	Predicted probability
Current asthma	$H = -1.9 + \text{Gender} * 0.83 + \text{Babysitter} * 0.06 - \text{Family network} * 0.24 - \text{alcohol in pregnancy} * 0.56 + \text{Ve} (\leq \text{median}) * 0.80$
A history of asthma	$0.94 + \text{Gender} * 0.05 - \text{Family network} * 0.15 - \text{alcohol in pregnancy} * 0.63 + \text{ParentalRhC} * 0.63 - \text{parental education} * 0.30 - \text{Resistance} (\leq \text{median}) * 0.51 + \text{Ve} (\leq \text{median}) * 0.91 + t_{\text{PTEF}/t_E} (\leq 0.20) * 0.32 + \text{Gender} * t_{\text{PTEF}/t_E} (\leq 0.20) * 1.00$
A history of rhinitis	$-1.9 + \text{Gender} * 0.62 + \text{economic stress} * 0.05 + \text{ParentalRhC} * 0.40 - \text{Cohabitation} * 1.32 - \text{Having siblings} * 0.80 - \text{economic stress} * \text{Gender} * 0.06$
Healthy	$0.34 - \text{Gender} * 0.78 + \text{alcohol in pregnancy} * 0.48 - \text{economic stress} * 0.08 - \text{Ve} (\leq \text{median}) * 0.51$

Baby sitter: how easy is it to get a babysitter during day time for an errand, Family network:

How easy will it be to contact family or friends for questions related to care of the baby?

Economic stress: how easy will it be to pay an unexpected bill in 1992/3 of 5000 NOK? All

three variables given on a visual analogue scale from 1-10 (1 being very easy and 10

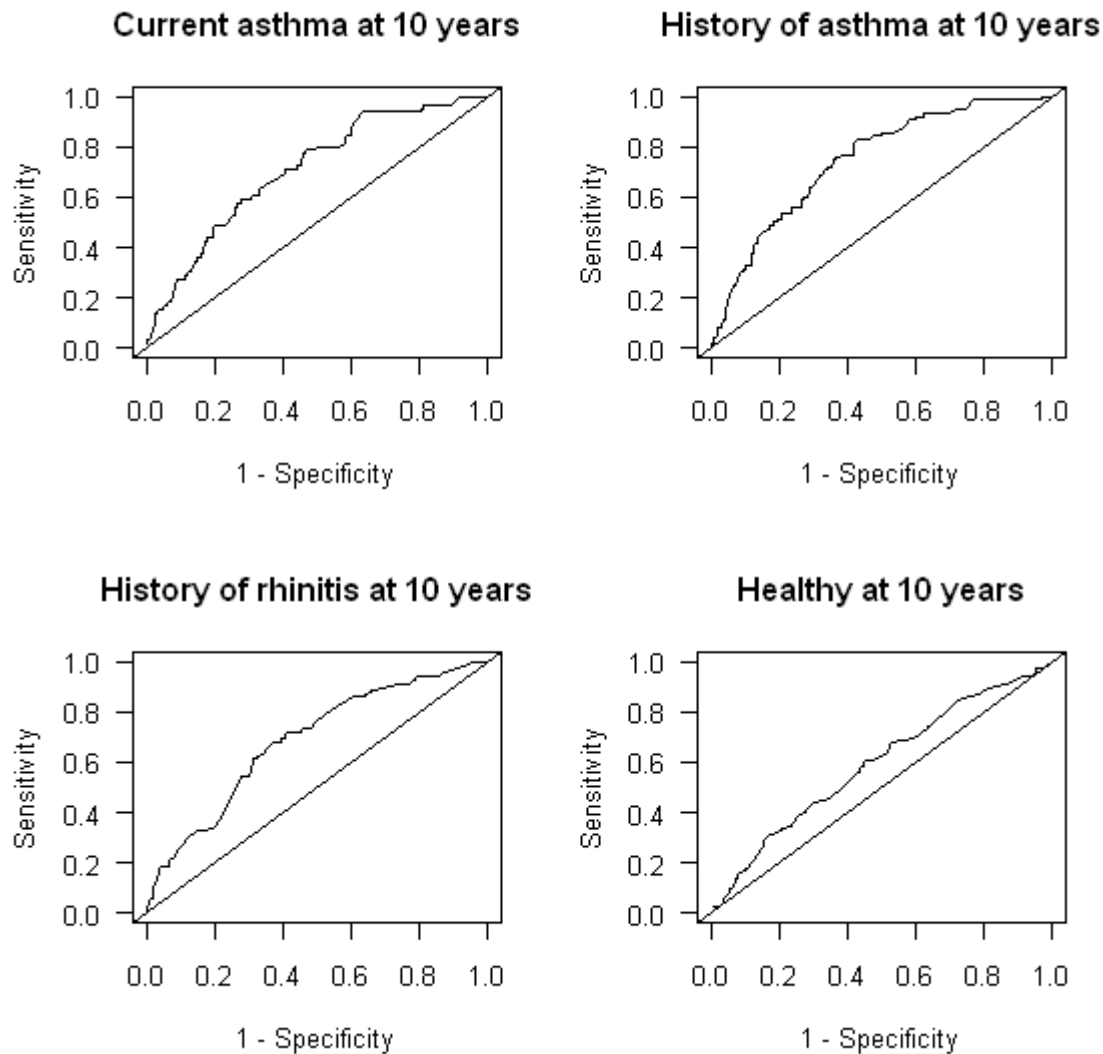
impossible), Parental education given for parent with the highest education: 1-6 (1 being 9-10

years at school and 6 University education), Alcohol: maternal use of alcohol in pregnancy,

Cohabitation: parental cohabitation.

Supplement figure 1.

Receiver operating curve (ROC) analyses describing the fit of the best model to predict the four outcomes at 10 years; a history of asthma, current asthma, a history of rhinitis and “healthy” (never wheeze, no history of rhinitis and no positive skin prick tests at 10 years).



References

1. Quanjer PH TG, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl. 1993;16:5-40.
2. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med. 2000 Jan;161(1):309-29.
3. Haland G, Carlsen KC, Sandvik L, Devulapalli CS, Munthe-Kaas MC, Pettersen M, et al. Reduced lung function at birth and the risk of asthma at 10 years of age. N Engl J Med. 2006;355(16):1682-9.