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Perinatal predictors of respiratory symptoms and lung function at a young adult age

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ABSTRACT: A longitudinal cohort of 2,957 babies, born in 1975–1978, was used to investigate whether perinatal factors predict respiratory morbidity at a young adult age.

In 1997, the presence of asthmatic (wheeze, nocturnal dyspnoea) and bronchitic (cough, phlegm, dyspnoea grade 3) symptoms and the level of lung function was determined in this cohort. The independent association between smoking during pregnancy, being first-born, birth weight and respiratory symptoms and lung function at young adult age was investigated using multiple regression models, taking other potential risk factors into account.

Of 1,568 responders, 608 (39%, aged 18–22 yrs) had at least one respiratory symptom. The young adults who had a mother that smoked during pregnancy had a significantly lower level of lung function than their nonintra-uterine exposed peers (regression coefficient (B) (standard error): peak expiratory flow (PEF) -0.257 (0.131) $L \cdot s^{-1}$; forced expiratory flow when 25% of the forced vital capacity has been exhaled (FEF_{25}) -0.290 (0.129) $L \cdot s^{-1}$), although they were not at increased risk of having respiratory symptoms. Young adults who were first-born had better levels of lung function (B (SE): forced expiratory volume in one second (FEV_1) 0.090 (0.042) L) and were less likely to have asthmatic symptoms (odds ratio (95% confidence interval): 0.58 (0.35–0.95)) than those not first-born. Low birth weight (FEV_1 -0.013 (0.004) L for a reduction of 100 g) was also predictive of reduced achieved levels of lung function at young adult age, independent of other potential risk factors, *e.g.* current smoking habits or familial predisposition.

This study adds to the knowledge of the role of perinatal factors, such as smoking during pregnancy, as important predictors of respiratory morbidity.

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There is increasing evidence suggesting that perinatal factors are associated with respiratory symptoms and the level of lung function in later life. For example, a clear relationship between low birth weight and reduced level of lung function in males aged 60–70 yrs has been described [1]. This observation is in accordance with a number of case-controlled studies that showed an increased prevalence of respiratory symptoms and reduced levels of lung function in school-aged children and in teenagers with a low birth weight [2–5]. MARTINEZ *et al.* [6] performed one of the few longitudinal birth cohort studies on this issue, and showed that recurrent wheeze at the age of 6 yrs was associated with male sex, being atopic, having a parent with asthma or allergy, maternal smoking and low socioeconomic status [6–8]. LEWIS *et al.* [9] followed-up a cohort of young infants and showed that males were more likely to wheeze at the age of 5 yrs showed when compared to females [9]. The same study showed that factors such as maternal smoking during pregnancy, bottle feeding, and low birth weight were also associated with an increased risk of wheezing. Moreover, the persistence of wheeze from age 5–16 yrs was associated with a young maternal age.

STRACHAN *et al.* [10] studied a cohort commencing at the age of 7 yrs. They showed that a young maternal age was a risk factor for developing asthma and wheezy bronchitis at an age of 7 or 16 yrs [10], and that a history of lower respiratory infections increased the likelihood of developing asthma and wheezy bronchitis. The persistence of wheeze up to the age of 23 yrs was only associated with a personal history of eczema or rhinitis. No proof was found that breast or bottle-feeding had an impact on the risk of developing asthma, wheezy bronchitis, or cough at an older age. Thus, the relevance and importance of perinatal factors for the development of respiratory symptoms and level of lung function at a young adult age is still unclear. Until now, no cohort has been followed-up from birth to adulthood, and data on the relationship between perinatal factors and maximal levels of lung function at a young adult age are completely lacking. Therefore, the relationships between perinatal factors and the development of respiratory

symptoms, and the level of lung function achieved at a young adult age, in a large well-defined cohort of babies followed-up for 18–22 yrs, were studied.

Methods

Sample selection

From 1975–1978 all newborn babies in the Obstetric dept of the University Hospital in Groningen were included in a prospective cohort study [11]. Detailed information on their perinatal conditions was collected. These data included: age of the mother, gravidity, marital status, diseases during pregnancy, active and passive smoking during pregnancy, socioeconomic status, educational level, birth weight and length (heel-crown). In the present study, the current respiratory health status of the children originally born in this cohort was determined. A questionnaire was mailed to all mothers and their children, now young adults, concerning respiratory symptoms, smoking habits, indoor exposures, family history of allergy and asthma, and querying whether the infants were breast and/or bottle-fed during the first 6 months of life. The database from the University Hospital of Groningen (Groningen, the Netherlands), was used to update the mothers' addresses (13%), as well as to exclude those mothers (n=24) and children (n=17) who had died. A total of 5,914 questionnaires were mailed to 2,957 mothers and 2,957 children. A random sample of the responders was invited to the medical hospital to perform lung function testing. A statistical programme determined a sex-stratified random order for inviting these young adults. The study was approved by the medical ethics committee of the University Hospital of Groningen. Subjects who performed a lung function test gave written informed consent prior to the test.

Perinatal factors

Birth weight was measured directly after birth and expressed in grams. A low birth weight was defined as the lowest 20% (quintile) of the distribution of weight, for males and females separately, of the total cohort (n=2957). This resulted in a cut-off value of 3,200 g for males and 3,050 g for females. The smoking habits of the pregnant females were monitored throughout pregnancy. For the children, smoking during pregnancy was defined as exposure to smoke *in utero*, through a mother who had smoked at any time during pregnancy. The average daily number of cigarettes smoked was recorded throughout pregnancy. Data on smoking during pregnancy, gestational age, and birth weight were stored in a computerised database.

Questionnaire

Data on current respiratory symptoms and smoking habits were collected in 1997 using the standardised questionnaire of the European Community Respiratory Health Survey (ECRHS) [12]. Subjects were considered to be symptomatic if they had experienced: wheezing or whistling, without having a cold, at any time in the last 12 months (wheeze); waking up due to an attack of shortness of breath at any time in the last 12 months (nocturnal dyspnoea); cough or phlegm, usually first thing in the morning, during the day or at night, in the winter; or shortness of breath when walking with other people of their own age on level ground (dyspnoea grade 3). Subjects who had wheeze and/or nocturnal dyspnoea were considered to have asthmatic symptoms [13]. The symptoms cough, phlegm, and dyspnoea grade 3 were grouped as bronchitic symptoms.

Questionnaire data were used to determine whether subjects had a positive family history for asthma or allergy (defined as having at least one parent with asthma or allergy) and if they had had a severe respiratory tract infection in the first year of life (defined as a positive answer by the mother to both the following questions: "Did your child have a severe respiratory tract infection in the first year of life?", and "Has this been confirmed by a doctor?").

Lung function

In 1998, a random sample of the questionnaire responders were subjected to lung function measurements. The ECRHS lung function protocol, which met with American Thoracic Society and European Respiratory Society guidelines, was used [12, 14, 15]. All forced expiratory manoeuvres were performed sitting, with the noseclip on, using a cardboard mouthpiece without teeth grips. Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), forced flow when 25, 50 and 75% of the forced vital flow has been exhaled (FEF_{25}, FEF_{50} and FEF_{75}) were recorded from at least two and up to five technically satisfactory manoeuvres [15]. The highest values were used in the analyses.

Statistical analysis

Differences in prevalence of asthmatic and bronchitic symptoms according to the presence or absence of perinatal factors (smoking during pregnancy, being first-born, low birth weight), and other potential risk factors (severe respiratory tract infection in the first year of life, current smoking, a familial history of asthma and allergy, sex) were tested using Chi-squared tests [16]. The independent association between perinatal factors and the presence of respiratory symptoms was investigated by means of multiple logistic regression [17]. In the 597 subjects who performed lung function tests, multiple linear regression was used to study the association of perinatal factors with the level of FEV_1, FVC, PEF, FEF_{25}, FEF_{50} and FEF_{75}. Plots of the residuals were inspected visually to verify model assumptions. The following perinatal factors were investigated simultaneously: smoking during pregnancy, being first-born, birth weight. All regressions were performed by taking

any other potential risk factors (severe respiratory tract infection in the first year of life, current smoking, having a parent with asthma or allergy (and asthmatic or bronchitic symptoms in the regressions on lung function)) and potential confounders (sex, current age and height) into account. Additional analyses were performed to check whether gestational age, maternal age, method of feeding (breast (exclusively, for at least 2 weeks) *versus* bottle (exclusively or combined with breast)) and environmental tobacco exposure in the first 5 yrs of life were potentially confounding factors. A $p<0.05$ was considered to be significant.

Results

Study population

Initially, 1,420 mothers and 1,300 children returned the questionnaires. After a second mailing to 1,350 nonresponders (excluding subjects who had moved (n=233), who refused to participate (n=8) or who had died (n=25 (19 mothers; six children)), a total of 1,568 mothers and their children had returned the questionnaires. Thus, of all the 2,724 (n=2957-233) questionnaires that probably arrived at the right address, the response of mother-child pairs was 59% (*i.e.* 1568/(2957-233-8-25)). The percentage of mothers who had smoked during pregnancy was significantly higher in the nonresponders compared to the responders (60.0 *versus* 50.1%). There were no significant differences with regard to other potential perinatal risk factors, such as low birth weight and young maternal age, between the nonresponders and the responders.

The characteristics of the questionnaire responders are shown in table 1. Smoking during pregnancy was common (50.1%). Babies who had been exposed to smoke *in utero* were significantly more likely to have a low birth weight than non-*in utero*-exposed babies (24.7 *versus* 16.6%), and tended to more commonly have a severe respiratory tract infection in the first year of life (15.0 *versus* 12.0%, p=0.068). Almost 17% of the males and 11% of the females had suffered from a severe respiratory tract infection in the first year of life. The prevalence of severe respiratory tract infection in the first year of life among low birth weight babies was not significantly different from normal-weight babies (14.8 *versus* 13.6%, data not shown in table 1).

The percentage of current smokers among the young adults was not significantly different between young males and females (37.0 and 35.0%, respectively). Young adults frequently reported to have a parent with asthma (15.8%) or allergy (51.7%).

Perinatal risk factors and respiratory symptoms

Figure 1 shows the prevalence of respiratory symptoms at a young adult age. The prevalence of asthmatic and bronchitic symptoms according to perinatal factors, severe respiratory tract infection in the first year of life, current smoking habits, family history of asthma or allergy and sex is shown in figures 2 and 3. Of 1,568 responders, 608 (39%) (18–22 yrs) had at least one respiratory symptom. Within those young adults who were first-born the prevalence of asthmatic symptoms was significantly lower than within those who were not (12.0 *versus* 16.0%). A mother who smoked during pregnancy and low birth weight (lowest quintile) were not associated with increased prevalence of respiratory symptoms in young adult life.

The prevalence of respiratory symptoms was significantly higher in those young adults who had had a severe respiratory tract infection in the first year of life when compared to those with a parent with asthma or allergy, and in current smokers. Females

Table 1. – Perinatal and other potential risk factors by sex

	Males	Females	Total
Subjects n	762	806	1,568
Age yrs	20.3±0.9	20.4±0.9	20.3±0.9
Mother smoked during pregnancy	355 (47.7)§	413 (52.4)	768 (50.1)
First-born	372 (48.8)	420 (52.1)	792 (50.5)
Birthweight g	3383±591*	3222±552	3300 (576)
Height at birth cm	506±28*	498±24	502 (26)
Maternal age yrs	26.4±4.5	26.0±4.3	26.2 (4.4)
Low maternal age (<20 yrs)	34 (4.5)*	21 (2.6)	55 (3.5)
Gestational age weeks median (range)	40 (28–44)	40 (29–44)	40 (28–44)
Breastfeeding#	63 (8.8)	80 (10.5)	143 (9.6)
Breastfeeding¶	125 (17.4)	144 (18.8)	269 (18.1)
Bottle feeding, exclusively	531 (73.9)	541 (70.7)	1072 (72.2)
Severe respiratory tract infection+	125 (16.8)*	87 (11.0)	212 (13.8)
Requiring doctor's consultation	119 (16.1)*	78 (9.9)	197 (12.9)
Requiring hospitalisation	22 (3.0)	19 (2.5)	41 (2.7)
Current smoking	280 (37.0)	278 (35.0)	558 (36.0)
Parent with asthma	106 (13.9)§	141 (17.5)	247 (15.8)
Parent with allergy	366 (48.0)*	445 (55.2)	811 (51.7)

Data are presented as mean±SD, n (%) or median (range). #: exclusively for at least 2 weeks; ¶: breast feeding with additional feeding; +: in the first year of life. Significant difference between males and females (tested by Chi-squared test or t-test). *: $p<0.05$; §$p<0.10$.

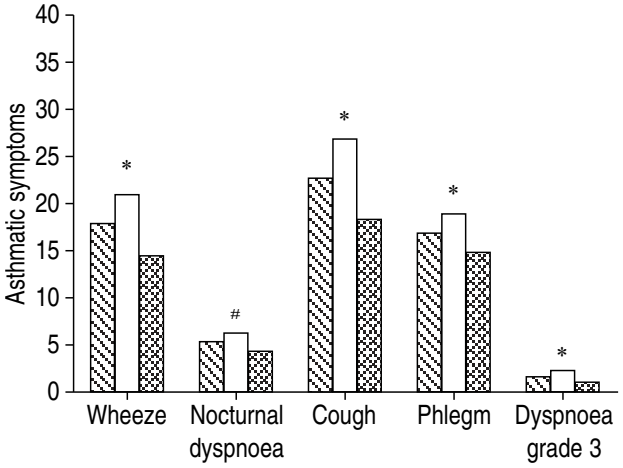

Fig. 1. – Prevalence of asthmatic symptoms (wheeze, nocturnal dyspnoea) and bronchitic symptoms (cough, phlegm, dyspnoea grade 3) in a cohort of 1,568 young adults (▨), and for females (□) and males (■) separately. *: $p<0.05$; #: $p<0.10$.

reported both asthmatic and bronchitic symptoms significantly more often than males.

When the independent effects of perinatal factors on the presence of respiratory symptoms at a young adult age were investigated, the results remained essentially the same (table 2). Taking other potential risk factors into account, being first-born was associated with a reduced risk of asthmatic symptoms. No significant interactions were found between the perinatal risk factors under study. Some of the other potential risk factors, however, were associated with an increased risk of respiratory symptoms.

Other potential risk factors and respiratory symptoms

Subjects who had had a severe respiratory tract infection in the first year of life were almost three times as likely to have asthmatic symptoms than subjects who had not suffered from such an infection. A severe respiratory tract infection in the first year of life also significantly increased the risk of having cough, or phlegm at a young adult age.

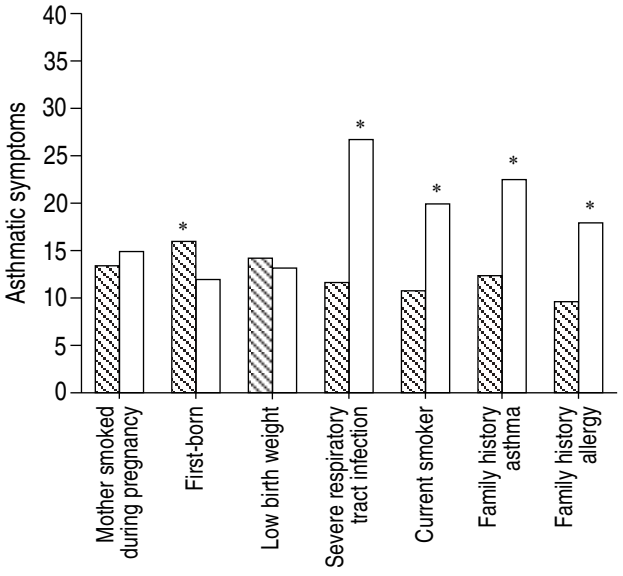

Fig. 2. – Prevalence of asthmatic symptoms (wheeze, nocturnal dyspnoea) according to perinatal factors and other potential risk factors in 1,568 young adults (▨: no; □: yes).*: $p<0.05$.

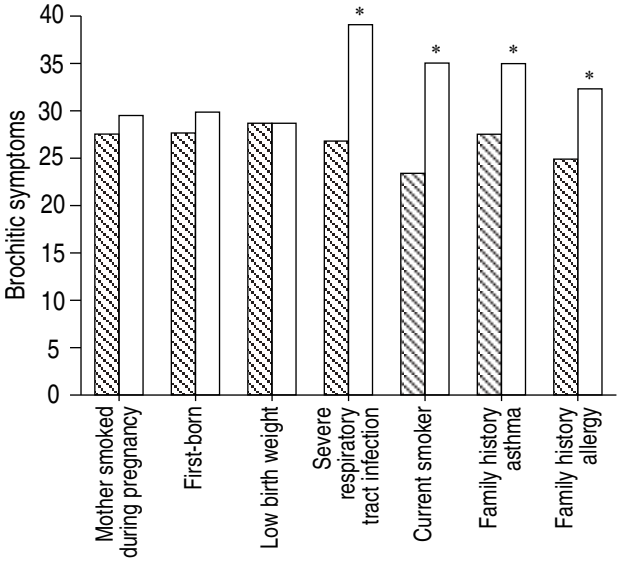

Fig. 3. – Prevalence of bronchitic symptoms (cough, phlegm, dyspnoea grade 3) according to perinatal factors and other potential risk factors in 1,568 young adults (▨: no; □: yes). *: $p<0.05$.

Current smokers were significantly more likely to have asthmatic or bronchitic symptoms. Those young adults with a positive family history of asthma or allergy had an increased risk of asthmatic symptoms.

Additional analyses with gestational age, maternal age, method of feeding and environmental tobacco exposure (see Methods section) included in this model, showed that these factors were not significantly associated with respiratory symptoms at a young adult age, nor did they influence the effect estimates as shown in table 2. No significant interactions were found between the perinatal risk factors and the other risk factors under study.

Perinatal factors and level of lung function

Complete and reliable lung function data were obtained in 590 (325 females) of the 597 subjects (99%) who performed lung function testing. Table 3 shows the results of the multiple linear regression analyses on FEV_1, FVC, PEF, FEF_{25}, FEF_{50}, and FEF_{75}, according to the presence or absence of perinatal factors, taking other potential risk factors into account, and adjusted for age, height and sex.

Smoking during pregnancy was associated with significantly lower values of PEF and FEF_{25} at a young adult age (table 3). The level of lung function achieved at a young adult age was related to the number of cigarettes the mother smoked during pregnancy. FEV_1 % predicted and PEF % pred [15] were significantly lower in those young adults whose mother had, on average, smoked >5 cigarettes·day^{-1}, compared to those whose mother had not smoked at

Table 2. – Independent associations of perinatal factors and asthmatic symptoms (wheeze, noctural dyspnoea) and bronchitic symptoms (cough, phlegm, dyspnoea grade 3) at a young adult age, with adjustment for other potential risk factors

	Asthmatic symptoms	Wheeze	Nocturnal dyspnoea	Bronchitic symptoms	Cough	Phlegm	Dyspnoea grade 3
Perinatal factors							
Mother smoked during pregnancy	0.91 (0.54–1.51)	0.73 (0.28–1.90)	0.60 (0.27–1.31)	0.98 (0.77–1.25)	1.09 (0.71–1.84)	1.15 (0.72–1.86)	0.91 (0.16–5.16)
Being first-born	0.58 (0.35–0.95)*	0.66 (0.27–1.65)	0.74 (0.35–1.57)	0.93 (0.64–1.36)	1.19 (0.80–1.79)	0.80 (0.51–1.27)	4.75 (0.54–41.78)
Birth weight, per 100 g increase	1.00 (0.95–1.04)	0.96 (0.88–1.05)	0.60 (0.27–1.31)	1.00 (0.96–1.03)	1.00 (0.97–1.04)	0.99 (0.95–1.03)	0.98 (0.84–1.14)
Other potential risk factors							
Severe respiratory tract infection[#]	2.76 (1.51–5.04)*	0.83 (0.30–2.29)	2.27 (0.93–5.53)[¶]	1.57 (0.92–2.71)	1.90 (1.08–3.33)*	2.04 (1.12–3.72)*	4.60 (0.77–27.48)[¶]
Current smoking	1.70 (1.02–2.84)*	1.01 (0.38–2.68)	1.75 (0.80–3.82)	2.23 (1.50–3.31)*	2.22 (1.46–3.37)*	1.80 (1.12–2.89)*	1.17 (0.20–7.06)
Family history asthma	2.07 (1.18–3.64)*	2.07 (0.71–6.08)	1.80 (0.77–4.20)	1.30 (0.80–2.12)	1.13 (0.67–1.90)	1.51 (0.97–2.64)	0.00 (0.00–1.89)
Family history allergy	1.84 (1.09–3.10)*	1.04 (0.41–2.66)	2.86 (1.18–6.91)*	1.36 (0.92–2.0)	1.24 (0.82–1.87)	1.07 (0.67–1.71)	1.61 (0.28–9.26)

Data are presented as odds ratio (95% confidence interval). COPD: chronic obstructive pulmonary disease. Multiple logistic regression analysis estimating the effect of perinatal factors (mother smoked during pregnancy, being first-born and birth weight) on respiratory symptoms, with adjustment for other potential risk factors (severe respiratory tract infection in the first year of life, current smoking habits, family history of asthma or allergy, sex (not shown), age (not shown). *: $p<0.05$; [¶]: $p<0.10$; [#]: in the first year of life. n=1,568.

Table 3. – Independent associations of perinatal factors and the lung function measurements at a young adult age, with adjustment for other potential risk factors

	FEV_1 L	FVC L	PEF $L \cdot s^{-1}$	FEF_{25} $L \cdot s^{-1}$	FEF_{50} $L \cdot s^{-1}$	FEF_{75} $L \cdot s^{-1}$
Perinatal factors						
Mother smoked during pregnancy	-0.061 (0.043)	-0.032 (0.048)	-0.257 (0.131)*	-0.290 (0.129)*	-0.127 (0.111)	-0.047 (0.069)
Being first-born	0.090 (0.042)*	0.089 (0.047)[¶]	0.358 (0.128)*	0.311 (0.126)*	0.092 (0.108)	0.023 (0.067)
Birth weight, per 100 g increase	0.013 (0.004)*	0.015 (0.005)*	0.021 (0.013)[¶]	0.043 (0.012)*	0.026 (0.011)*	0.011 (0.007)[¶]
Other potential risk factors						
Severe respiratory tract infection[#]	-0.170 (0.062)*	-0.075 (0.070)	-0.627 (0.189)*	-0.665 (0.187)*	-0.408 (0.160)*	-0.177 (0.100)[¶]
Current smoker	0.030 (0.046)	0.098 (0.052)[¶]	0.035 (0.140)	0.117 (0.139)	-0.100 (0.119)	-0.093 (0.74)
Family history asthma	-0.008 (0.055)	0.001 (0.062)	-0.403 (0.169)*	-0.440 (0.167)*	-0.230 (0.144)	0.005 (0.089)
Family history allery	0.048 (0.042)	0.008 (0.048)	0.106 (0.129)	0.227 (0.128)[¶]	0.143 (0.110)	0.071 (0.086)
Asthmatic symptoms	-0.085 (0.061)	0.004 (0.068)	-0.171 (0.186)	-0.312 (0.184)[¶]	-0.303 (0.158)[¶]	-0.195 (0.098)*
Bronchitic symptoms	-0.093 (0.048)[¶]	0.038 (0.054)	-0.324 (0.146)*	-0.419 (0.144)*	-0.208 (0.124)[¶]	-0.149 (0.077)[¶]

Data are presented as B (SE). FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow; FEF_{25}, FEF_{50}, FEF_{75}: forced expiratory flow when 25%, 50% and 75% of the forced expiratory vital capacity has been exhaled. Multiple linear regression analysis estimating the effect of perinatal factors (mother smoked during pregnancy, being first-born and birth weight) on level of lung function, with adjustment for other potential risk factors (severe respiratory tract infection in the first year of life, current smoking, asthmatic and bronchitic symptoms, family history for asthma or allergy, sex (not shown), age (not shown), height (not shown). *: $p<0.05$; [¶]: $p<0.10$; [#]: in the first year of life. n=590.

all during pregnancy. The PEF % pred was even significantly decreased in those young adults whose mother had smoked 1–5 cigarettes daily, compared to those whose mother had not smoked at all during pregnancy.

The level of lung function was significantly lower in those young adults with lower birth weights. For each 100 g increase in birth weight, the FEV_1 increased by a mean of 0.013 L, FVC by 0.015 L, FEF_{25} by 0.043 $L \cdot s^{-1}$, and FEF_{50} by 0.026 $L \cdot s^{-1}$. Adjustment for gestational age did not change the associations between birthweight and lower level of lung function. On average, FEV_1 (0.090 L), PEF (0.358 $L \cdot s^{-1}$) and FEF_{25} (0.311 $L \cdot s^{-1}$) were significantly higher in first-borns compared to those who were not first-born. No significant interactions were found between the perinatal risk factors under study.

Other potential risk factors and level of lung function

Subjects with a severe respiratory tract infection in the first year of life had significantly lower levels of lung function than those who had not suffered from such an infection.

Young adults with a positive family history for asthma or with bronchitic symptoms had significantly lower levels of lung function than those without these characteristics.

Additional analyses with gestational age, maternal age, method of feeding and environmental tobacco exposure (see Methods section) included in the model, showed that these factors were not significantly associated with the achieved level of lung function at a young adult age and did not influence the effect estimates as shown in table 3.

No significant interactions were found between the perinatal risk factors and the other risk factors under study.

Discussion

The results of the current study showed that smoking during pregnancy and low birth weight increased the risk of having a diminished level of lung function at a young adult age, taking genetic predisposition and personal exposures into account. It is striking that perinatal events which occurred 20 yrs ago had such a large impact on the current respiratory health status in young adults.

Previous studies focused on early life events (respiratory tract infection, environmental tobacco smoke exposure), whereas others mainly studied perinatal factors such as birth weight and gestational age, without specifically taking early life events into account [18–21]. However, birth weight is the result of genetic as well as environmental factors that occur during pregnancy. For example, it is well known that exposure to smoke during pregnancy is negatively related to birth weight.

This is the first study that has simultaneously taken into account perinatal and early life factors, smoking habits and familial predisposition, and focused on their joint relationship to respiratory morbidity at a young adult age. This allowed for the assessment of whether these factors, which occur at different stages during lung development, modified each other's effect on respiratory morbidity at a young adult age. When interpreting the result of the current study, it can be concluded that there are no indications that such a modification occurs. For example, a negative effect of smoking during pregnancy on the level of lung function achieved at a young adult age was observed regardless of the negative effect of a low birth weight, or having had a severe respiratory tract infection in the first year of life.

Unfortunately, contrary to the perinatal data, the data on some of the other potential risk factors were collected concomitantly with data on current respiratory morbidity, therefore there is possibility of preferential recall bias. For example, mothers of symptomatic young adults may better recall that their child had a severe respiratory tract infection in early life. It cannot be excluded that such a bias partly accounts for the association that was found between a severe respiratory infection in the first year of life and the current reporting of respiratory symptoms. However, it seems unlikely that this type of bias accounts for the association found with reduced levels of lung function [22]; the association was present irrespective of whether the young adults were symptomatic or not.

Low birth weight has been shown to be associated with reduced levels of lung function at an advanced age. STEIN *et al.* [18] showed that in a 40–50-yr-old population a lower FEV_1 was associated with a lower birth weight. FEV_1 and FVC were lower in males who smoked, but the associations with size at birth were independent of smoking. Similar associations were found between birth weight and level of lung function, although the cohort consisted of substantially younger males and females.

The clear association between low birth weight and lower levels of lung function in children has been explained by a number of sequential mechanisms. MARTINEZ *et al.* [23] have suggested that the intrauterine factors that retard foetal weight gain may irrecoverably constrain the growth of the airways. Children whose mothers smoked during pregnancy are therefore likely to have decreased levels of lung function at birth [24], which may predispose to lower respiratory tract infections with wheezing in the first 2 yrs of life [23] and the development of respiratory morbidity [25]. The current study shows that babies that were exposed to intrauterine smoke were more likely to have had a severe respiratory tract infection in the first year of life, both factors being independently and negatively associated with diminished lung function in the cohort of young adults. This confirms earlier work showing that respiratory tract infections in early childhood are associated with reduced levels of FEV_1 in males aged 60–70 yrs [26].

Selection bias as a consequence of severe disease is unlikely, because the respiratory conditions under study are probably not fatal at this young age. Likewise, responder bias does not seem to have influenced the results, because the prevalence of respiratory symptoms in the current study population is not

substantially different from that in a random population [27]. Whether or not young adult questionnaire responders were different from the nonresponders with regard to their perinatal risk factors was checked, using the data that were collected in the mid 1970s. Responders were less likely to have been exposed to smoke *in utero* than nonresponders. Because smoking during pregnancy was associated with an increased risk for severe respiratory tract infection in the first year of life, it might indirectly lead to respiratory morbidity at a young adult age. This association may be causal. However, the magnitude of the effect of low birth weight on respiratory symptoms, or lung function, did not change when severe respiratory tract infection in the first year of life was taken into account. There was also no significant interaction between smoking during pregnancy and low birth weight, or between smoking during pregnancy and severe respiratory tract infection in the first year of life.

A number of studies have shown associations between maternal age and respiratory morbidity in infants. Younger mothers are more likely to have children who develop wheezing illnesses in early life [28], asthma or other respiratory diseases. This suggests that lung development may differ between offspring from younger and older mothers. Competition between maternal growth and foetal growth may possibly explain these differences, which results in a less optimal maturation of the children at birth. However, the results do not support this hypothesis; there was no relationship between a low maternal age and the risk of having respiratory symptoms or a low level of lung function at a young adult age. Thus, in the cohort, having a teenage mother did not seem to negatively affect respiratory heath at a young adult age. However, this lack of association might be due to a lack of power; the number of teenage mothers in the study was very low (3.5% aged <20 yrs).

There was no association between breastfeeding for at least 2 weeks and respiratory health at a young adult age. To check whether this was due to the definition of breastfeeding (exclusively, for at least 2 weeks), longer periods of breastfeeding were analysed (1, 2, 3 months), but were still unable to show associations with respiratory health in the young adults. This may have been due to the lack of power, since the number of children that were breastfed was limited.

Although it is well recognised that genetic predisposition and personal exposures, such as cigarette smoking, are major determinants of respiratory morbidity, interactions between these factors cannot fully explain the respiratory health status. Smoking during pregnancy, low birth weight and severe respiratory tract infection in the first year of life are significant predictors of respiratory symptoms and diminished level of lung function at a young adult age.

The underlying mechanisms that can explain these associations are still poorly understood. It has been suggested that the maternal blood pressure level, or a maternal-foetal hormonal imbalance might influence foetal, and subsequently, adult metabolism, and reduce maturation of the foetal and newborn′s lung [29].

The current study confirms results from previous studies that suggested that birth weight and smoking during pregnancy were associated with respiratory morbidity later in life. It provides new insights into the relationship between perinatal and other potential risk factors and respiratory morbidity because of the novel age group under study. The data provided a unique opportunity to study these associations, as the collection of all pre- and perinatal risk factors has been assessed in a standardised way during pregnancy and around birth. From the present data it can be suggested that further epidemiological studies should particularly focus on the prenatal interactions between the pregnant mother and the foetus, because increased knowledge of this developmental phase, may provide a new insight in to the origin of respiratory morbidity in later life.

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