



Is birth weight related to lung function and asthma symptoms in Nordic-Baltic adults?

B.N. Lærum^{a,b,*}, C. Svanes^c, A. Gulsvik^a, M. Iversen^d,
H.R. Thorarinsdottir^e, T. Gislason^e, R. Jögi^f, E. Norrman^g,
M. Gunnbjörnsdottir^h, T. Wentzel-Larsen^b, C. Janson^h, E. Omenaas^b

^aDepartment of Thoracic Medicine, Haukeland University Hospital, N-5021 Bergen, Norway

^bCentre for Clinical Research, Haukeland University Hospital, N-5021 Bergen, Norway

^cDepartment of Internal Medicine, University Hospital Haraldsplass, N-5009 Bergen, Norway

^dDepartment of Internal Medicine, Rigshospitalet, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark

^eDepartment of Pulmonary Medicine, Landspítali University Hospital, I-105 Reykjavik, Iceland

^fLung Clinic of Tartu University Clinics, EST-51014 Tartu, Estonia

^gDepartment of Pulmonary Medicine and Allergology, University Hospital of Northern Sweden, SE-901 85 Umeå, Sweden

^hDepartment of Medical Sciences, Respiratory Medicine and Allergology, Uppsala University, Akademiska Sjukhuset, SE-751 85 Uppsala, Sweden

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Summary Studies of birth characteristics and respiratory outcomes show contradictory findings. We wanted to investigate the association of birth weight with adult lung function as well as asthma symptoms while addressing the influence of demographic and environmental factors.

Data was collected from the birth records of 1683 men and women born in 1947–1973 who were included in 6 Nordic-Baltic population samples investigated within the European Community Respiratory Health Survey (ECRHS).

In the adults, an increase in birth weight from below 2500 g to above 4000 g was associated with an increase from 96% to 104% predicted one-second forced expiratory volume ($P < 0.01$) and from 100% to 107% predicted forced vital capacity ($P < 0.01$). However, birth weight was not associated with symptoms of asthma. After adjustment for birth length, gender, age, study centre, adult BMI, allergic rhinitis, parental and adult tobacco smoke exposure in multivariate regression analyses, birth weight was not associated with adult lung function or asthma symptoms. Further sub-sample analyses revealed no influence of gestational age, gender, age or geographical area.

In this historic prospective cohort study an association was neither found between birth weight and adult lung function nor between birth weight and asthma symptoms.

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*Corresponding author. Department of Thoracic Medicine, Haukeland University Hospital, N-5021 Bergen, Norway. Tel.: +47-55973245; fax: +47-55975149.

E-mail address: birger.lerum@helse-bergen.no (B.N. Lærum).

Introduction

Adult illness can often be traced back to influences early in life. Intrauterine conditions causing growth retardation might affect the lung development irreversibly.¹ Forsdahl² observed in 1977 that impaired childhood living conditions were associated with reduced adult health status for persons born in 1925–59. Barker et al.³ showed a positive association between birth weight and adult forced expiratory volume in one second (FEV₁) in a study of 59–70 year old men born in 1920–30. A positive association was also found between birth weight and lung function in 5–11 year old British children born in 1979–85⁴ and in 18–22 year old Dutch subjects born in 1975–78.⁵ However, the association of birth weight and lung function could not be confirmed in a UK study of 50–65 year old subjects born in 1921–35,⁶ or in studies of adolescents born in 1975–77 in the UK⁷ and in 1972–73 in New Zealand.⁸ In a recent, large population study of adolescents born in 1976–84 in Norway, no association of birth weight and -length with lung function or symptoms of asthma was found.⁹

An inverse association of asthma symptoms and birth weight was found in studies of Israeli¹⁰ and Swedish¹¹ male recruits born in 1967–71 and in 1973–75, respectively, in the 1970 British Cohort Study¹² and in 20–24 year old Norwegian men and women born in 1967–72.¹³ However, in children from New Zealand, less asthma was observed in those with low birth weight while more asthma was observed in those with a greater birth length.¹⁴

The referred studies included subjects born in 1920–1985, age groups ranging from childhood to old age and some studies included male subjects only. All previous studies were limited to one geographical area. In most studies either asthma-like symptoms, diagnosis of asthma or lung function were chosen as outcome variables.

Using a standardized methodology in a prospective study of men and women born in 1947–73 in Denmark, Estonia, Iceland, Norway and Sweden, our objectives were, firstly, to study whether birth weight predicted level of adult lung function or symptoms of asthma. Secondly, we questioned whether gender and age influenced such associations. Finally, we asked whether such associations were influenced by geographic area.

Methods

The European Community Respiratory Health Survey (ECRHS)

The data used in this paper from the Nordic-Baltic countries came from a sub-study of the ECRHS.

Samples of men and women aged 20–44 years were drawn randomly within pre-existing municipal boundaries with at least 150 000 inhabitants. Informed consent was obtained, and the Regional Ethics Committees approved the study. The methods of the ECRHS have been described fully elsewhere.¹⁵ In short, random sub-samples of subjects who had completed the screening questionnaire (stage 1) were invited to attend the clinical part (stage 2) of the study. In a structured interview, detailed questions were asked about symptoms of asthma, allergies, current and parental tobacco smoking and education. Spirometry was performed in a standardized manner¹⁶ including measuring height (cm) and weight (kg). The European Community for Steel and Coal Company (ECSC) reference values were used, giving values for FEV₁ and forced vital capacity (FVC) as percent predicted, adjusting for age, gender and height.¹⁷ Item non-response was present for several variables in the questionnaire and lung volume measurements (7–8%).

Birth information

A Nordic-Baltic birth weight project was initiated in six centres participating in the ECRHS; Århus in Denmark, Bergen in Norway, Reykjavik in Iceland, Umeå and Uppsala in Sweden and Tartu in Estonia. In these centres, 4440 subjects who had completed the screening questionnaire (stage 1) were invited to attend the clinical part (stage 2), of whom 3201 responded (72%). Co-workers at the six study centres searched for birth records of the responders in hospitals and the main birth wards. No attempt was made to trace birth records of subjects born outside the municipality and later moving into the study area. We were unable to identify subjects who had changed their family name and whose mothers' names were unknown. Women were not traced in Tartu. Subjects born in 1967 or later in Bergen were identified through a national person identification number in the Norwegian Medical Birth Registry.¹⁸ Information on birth weight, birth length and gestational age was collected from the identified birth records. In the birth records, prematurity was defined as birth before the 36th week of gestation. Newborns in Århus, Bergen, Umeå and Uppsala ($n = 1270$) were classified as preterm or term born. Information on gestational age (days) was available in Bergen, Umeå and Uppsala ($n = 503$). Birth weights corresponding to the 2.5th percentiles for given gestational age (weeks) in the Norwegian reference values, were used as cut points for defining small for gestational age.¹⁹ Birth weight was measured

using mechanical “balance weights” (grams) and crown–heel length by using a measuring board with a movable foot-piece (cm) when stretching the newborn baby. The information in the birth records was recorded at the time of the births. Therefore, this analysis of birth characteristics and adult respiratory health status was designed as a historic prospective cohort study.

Data handling and statistical analysis

Analysis of variance (ANOVA) was used for comparing means of birth weight, birth length and adult lung function since these showed a normal distribution. χ^2 tests were used for comparing proportions. The relationships of birth weight, birth length and adult lung function adjusting for possible confounders (gender, age, prematurity, study centres, adult body mass index (BMI), allergic rhinitis, parental and adult tobacco smoke exposure) were analysed by linear regression. A logistic regression model, including the same potential confounders, was used to assess the effects of birth weight and birth length on symptoms of asthma. Meta analyses were used to investigate heterogeneity. The effects of possible measurement errors were analysed with simulations. We used SPSS 9.0–11.0 (SPSS for Windows, Release 11.0, SPSS Inc.) for most analyses, but the statistical package *R*²⁰ for the meta analyses and simulations. The significance level was chosen as 0.05.

Results

Population characteristics

Of the 3201 ECRHS responders (stage 2) from the six centres, 1683 subjects (53%) were identified in local birth records and data registries in the six Nordic-Baltic centres. Birth data for 636 ECRHS non-responders (stage 2) were collected in Reykjavik, Tartu and Bergen. We found no difference in mean birth weight between the responders and non-responders, neither for boys (3577 vs. 3542 g, $P = 0.58$) nor for girls (3442 vs. 3475 g, $P = 0.66$). No differences were found between the ECRHS-responders with or without birth information with respect to smoking habits ($P = 0.34$) or gender ($P = 0.10$). In addition, different levels of items non-response was present for both outcome and predictor variables, ranging from 0% (wheeze) to 25% (prematurity). Thus the numbers of subjects included in the analyses presented in Tables 2 and 3 are lower than in Table 1.

Table 1 shows the characteristics of the study populations by centres. Mean weight and length at birth, tobacco smoke exposure, allergic rhinitis and respiratory symptoms varied between the six centres. Adult $FEV_{1\%predicted}$ ranged from 97.2 in Bergen to 108.0 in Tartu ($P < 0.001$). Adult $FVC\%_{predicted}$ ranged from 100.3 in Bergen to 111.5 in Uppsala ($P < 0.001$).

Univariate analyses

Increase in birth weight from below 2500 g to above 4000 g was associated with an increase from 96 to 104 in $FEV_{1\%predicted}$ ($P < 0.01$) and from 100 to 107 in $FVC\%_{predicted}$ ($P < 0.01$). An increase in birth length from <50 to >52 cm was associated with an increase from 100 to 103 in $FEV_{1\%predicted}$ ($P < 0.01$) and from 103 to 106 in $FVC\%_{predicted}$ ($P < 0.01$). There was no association between birth weight and the $FEV_{1\%predicted}/FVC\%_{predicted}$ ratio (data not given). Asthma-like symptoms tended to have U-shaped associations with birth weight and birth length (Table 2).

Multivariate analysis

After adjustment for birth length, gender, age, study centre, adult BMI, allergic rhinitis, parental and adult smoking, there was no significant association between birth weight and level of adult lung function or between birth weight and symptoms of asthma (Table 3).

Prematurity, maternal age and age at completed education had no significant effect on lung function or asthma symptoms in the multiple regression analysis. Including these variables, or in addition other respiratory symptoms, did not alter the magnitude of the effect estimates presented in Table 3.

In univariate or multivariate analyses of a subsample ($n = 490$), we found no significant associations between the small for gestational age dichotomy (2.5th percentile) and any of the adult respiratory outcomes (wheeze, wheeze with shortness of breath, wheeze without a cold, woken with tightness, $FEV_1\%$ or $FVC\%$).

Considering younger subjects in our sample, lower birth weight tended to be associated with more wheeze and lower lung function, while no such association was found in the older subjects. Differences by age were, however, not significant in analyses of interaction. We observed no significant differences by study centre (Figs. 1 and 2) or gender with regard to analyses of birth weight and adult respiratory health.

Table 1 Birth and adult characteristics, tobacco smoke exposure, allergic rhinitis, adult lung function and respiratory symptoms in 20–47 year old responders of a Nordic-Baltic population study.

	<i>n</i>	Århus	Bergen	Reykjavik	Tartu*	Umeå	Uppsala	All
Female % of total	1622	54%	47%	49%	0%	58%	47%	47%
Preterm births**	1270	8%	2%	—	2%	0%	4%	3%
Mean birth weight (g)								
Male	867	3488	3544	3676	3711	3575	3480	3571
Female	755	3323	3433	3519	—	3395	3481	3445
Mean birth length (cm)								
Male	866	52.0	50.9	51.7	50.7	51.3	50.6	51.1
Female	752	51.5	50.3	51.1	—	50.2	50.3	50.6
Parental tobacco smoking								
1 parent or more	1680	87%	72%	74%	65%	73%	71%	73%
Pregnancy	1655	21%	16%	19%	3%	20%	21%	18%
Adult tobacco smoke exposure†								
Current	645	40%	45%	40%	46%	22%	28%	39%
Ex-Environmental	313	17%	15%	23%	20%	20%	21%	19%
Never	257	23%	14%	21%	12%	8%	11%	15%
Never	461	21%	26%	17%	21%	50%	40%	28%
Mean BMI (kg/m ²) (SD)	1561	23.3 (3.9)	24.2 (3.7)	24.2 (3.5)	23.7 (2.8)	22.7 (3.2)	23.3 (3.6)	23.8 (3.7)
Obesity % (BMI > 30 kg/m ²)	87	6.0%	7.0%	6.9%	2.8%	2.9%	2.5%	5.6%
Mean FEV ₁ % predicted (SD)	1559	97.8 (13.0)	97.2 (11.5)	103.8 (12.5)	108.0 (15.2)	106.3 (12.1)	107.9 (12.7)	101.7 (13.1)
Mean FVC% predicted (SD)	1556	105.6 (12.7)	100.3 (11.8)	105.2 (12.4)	105.9 (16.0)	108.1 (14.8)	111.5 (13.3)	104.7 (13.4)
Allergic rhinitis	1672	18%	16%	24%	13%	31%	31%	21%
Wheeze‡	1682	33%	24%	17%	20%	26%	28%	24%
Wheeze with shortness of breath‡	1678	10%	13%	5%	4%	14%	13%	10%
Wheeze without a cold‡	1675	18%	14%	10%	14%	15%	13%	14%
Woken with tightness in chest‡	1674	10%	12%	10%	11%	12%	11%	11%

*Men only.

**Preterm birth defined in the birth records as gestational age below 36 weeks.

†Exclusive categories.

‡In the last 12 months.

Table 2 Adult lung function and respiratory symptoms according to birth characteristics, tobacco smoke exposure and allergic rhinitis in responders of a Nordic-Baltic population study.

	<i>n</i>	Mean FEV ₁ % _{predicted}	Mean FVC% _{predicted}	Wheeze (%) [*]	Wheeze with shortness of breath (%) [*]	Wheeze without a cold (%) [*]	Woken with tightness in chest (%) [*]
Gestational age							
Preterm ^{**}	37	98	104	22	14	8%	8
Term	1135	101	105	25	12	14	11
Birth weight (g)							
<2500	49	96	100	16	6	6	8
2500–2999	164	100	104	27	10	13	14
3000–3499	593	101	104	24	11	14	10
3500–3999	491	102	105	26	11	15	10
>4000	262	104	107	20	8	12	13
Birth length (cm)							
<50.0	372	100	103	23	11	13	11
50.0–51.9	584	102	104	25	11	13	10
>52.0	599	103	106	24	9	15	13
Parental tobacco smoking							
1 parent or more	1124	101	105	25	11	14	11
None	406	103	104	22	9	12	12
Adult tobacco smoke exposure [†]							
Current	643	99	103	38	15	21	13
Ex-	313	105	108	18	7	11	7
Environmental	257	102	104	14	7	7	12
Never	461	103	105	14	9	9	10
Allergic rhinitis							
Yes	341	104	106	36	18	23	18
No	1204	101	104	21	8	11	9

*In the last 12 months.

^{**}Preterm birth defined in the birth records as gestational age below 36 weeks.[†]Exclusive categories.

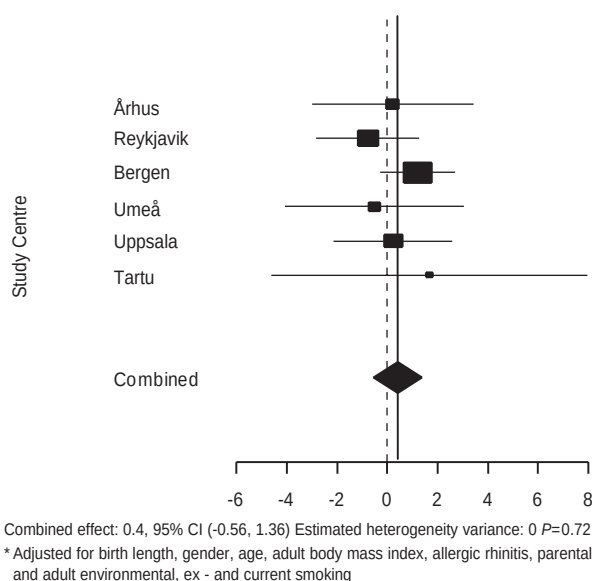
Table 3 Adjusted effects of birth weight on forced expiratory volume in one second (FEV₁%_{predicted})*, forced vital capacity (FVC%_{predicted})* and respiratory symptoms** in adult responders of a Nordic-Baltic population study.

	<i>n</i>	Birth weight/500 (g)	
		Regression coefficients	95% CI
FEV ₁ % _{predicted}	1493	0.45	−0.52–1.41
FVC% _{predicted}	1494	0.47	−0.52–1.46
		Odds ratios	95% CI
Wheeze [†]	1494	0.98	0.81–1.19
Wheeze with shortness of breath [†]	1491	0.92	0.71–1.20
Wheeze without a cold [†]	1488	0.93	0.74–1.18
Woken with tightness in chest [†]	1487	0.87	0.67–1.12

*Multivariate, linear regression analyses of birth weight with regression coefficients (95% confidence interval), adjusted for birth length, gender, age, study centre, adult body mass index, allergic rhinitis, parental and adult environmental, ex- and current smoking.

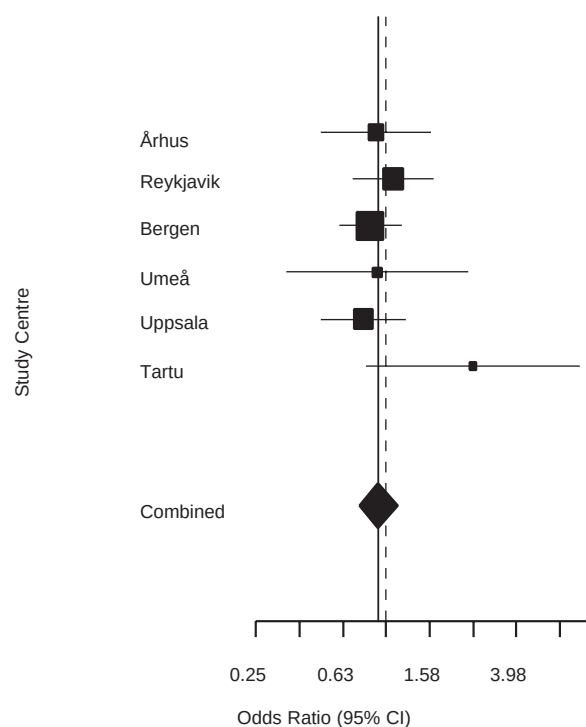
**Multivariate, logistic regression analyses of birth weight with odds ratios (95% confidence interval), adjusted for birth length, gender, age, study centre, adult body mass index, allergic rhinitis, parental and adult environmental, ex- and current smoking.

[†]In the last 12 months.

**Figure 1** Meta analysis of centre variation on the association* of birth weight/500 g and adult level of one second forced expiratory volume.

Discussion

In this Nordic-Baltic retrospective cohort study of young adult men and women born in 1947–73, we observed that birth weight did not predict level of lung function or symptoms of asthma. This did not vary by age or gender. Furthermore, the association of birth weight and adult respiratory health did not vary between the study centres.

**Figure 2** Meta analysis of centre variation on the association* of birth weight/500 g and adult “wheeze” in the last 12 months.

Our overall results are in agreement with those studies not showing an association of birth weight and respiratory outcomes.^{6–9} However, in some

subgroups of our study an inverse association of birth weight with adult lung health was indicated, being in line with other studies.^{3-5,10-13} Thus, the discrepancy in the literature is reflected in this multi-centre study.

Methodological considerations

The mean age in subjects without birth information was 34 years and in subjects with birth information 32 years. This might be due to more complete information in Bergen for those born after 1967 when the Norwegian Medical Birth Registry was established. There were, however, no relevant differences in associations between birth weight and respiratory outcomes when excluding the subjects from Bergen. Smoking habits and gender did not differ in responders with or without birth information. Furthermore, mean birth weight did not vary in non-responders and responders. We thus believe that the responders with information from birth records in our sample ($n = 1683$) are not substantially different from the stage 2 responders of the ECRHS ($n = 3201$) or the initial random sample. Bias regarding social class is unlikely since all the pregnant mothers living in the six study areas were referred to the local public hospital regardless of social class.

Many studies of birth characteristics and adult lung health are limited by the high percentage of non-responders varying from 21% to 77%.³⁻¹⁴ Another limitation is the loss to follow-up of subjects who have moved out of the study area. Subjects who move out of the study area may differ from the rest of the population with regard to demographic characteristics. In addition this may vary by geographical area. Thus, complex patterns of selection could possibly explain the discrepancy in the literature. Furthermore, publication bias tending not to publish negative results is another possible contributor to discrepancy. A multi-centre study, such as the present one, where centres are included regardless of whether the results are considered interesting or not, is thus of importance.

Measurement errors in the birth characteristics may exist. Measurement of birth weight, however, is considered accurate, although depending on the calibration and quality control of the different mechanical weights. Measured birth length of the newborn babies, however, depends on the extent of stretching and may therefore be less accurate. In addition, analyses of birth length in the present study revealed a digit point preference. For example, a birth length of 50.0 cm was much more frequent than 50.2 cm. When the measurement error of birth length

was artificially increased in simulation analyses, the effect estimates of birth weight on respiratory outcomes increased, while the effect estimates of birth length decreased. This could in our sample, indicate an overestimation of the association between birth weight and respiratory outcomes, but an underestimation of the association between birth length and respiratory outcomes.

Camargo et al.²¹ showed a strong, positive and independent association between adult BMI and adult-onset asthma in a large prospective cohort study of female nurses. In our study, the inclusion of adult BMI in the multivariate analysis did not, however, alter the effect estimates of birth weight and birth length on adult symptoms of asthma in our study.

Information on environmental influence from early life to adulthood, family status and adult lung health was obtained through a structured interview using the ECRHS questionnaire. Thus, subjects were asked about their parents' smoking habits 20–44 years earlier, implying possible recall bias. However, parental tobacco smoke exposure was not a significant confounder in our analyses. Information on self-reported smoking habits in adults is found to have high validity in Nordic general population surveys,²² although residual confounding may exist.

Environmental influences on the relationship between birth weight and lung function as well as symptoms of asthma

In the present study there was an indication of increased effect of birth weight on respiratory outcomes with younger age or with more recent birth period. This could imply a wearing off effect with older age in our study. Barker et al.³ showed positive association between birth weight and adult lung function in elderly men, thus indicating reduced effect of birth weight on respiratory outcomes with older age to be unlikely.

Environmental factors related to poor intrauterine growth, might have changed during the period from 1947 to 1973 when our subjects were born. During this period, perinatal mortality fell from 24.5 to 16.4 per 1000 live births (Statistics Norway). Since modern neonatology has improved the survival rate particularly among low birth weight and premature infants with poor pulmonary development increased survival of the low birth weight babies might affect the association between birth weight and adult respiratory health. However, since the percentage of the premature born subjects in our study was only 3%, it is unlikely to have affected our results

substantially. In addition, no association was found between the small for gestational age dichotomy and respiratory health outcomes.

Factors such as mother's diet, medication, health care, working conditions and indoor and outdoor environment can influence the growth and development of the bronchial tree and the lungs early in life.²³ Information about these factors was not available in our study and could not be investigated. However, geographical area could be considered a proxy variable for differences in environment, but meta analyses did not show significant heterogeneity across the six centres in the present study.

Our study seems to be limited by the crown-heel measurement error of birth length as well as heterogeneity in birth cohorts from 1947 to 1973 (or age 20–44 years), non-response and geographical variation. Further research on the association between birth weight and respiratory health should therefore include a more exact measurement of birth length, for example crown-rump length. The measurement of crown-rump length is performed without stretching the newborn child and is comparable with prenatal ultrasonographic measurement of intrauterine growth.²⁴ In addition, future studies of birth characteristics and respiratory health should be designed as prospective, longitudinal cohort studies with high response rates.

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