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10.1002/ppul.23448

Link to publication record in Explore Bristol Research

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Effect of early term birth on lung function and respiratory symptoms in childhood and adolescence

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Keywords: Avon Longitudinal Study of Parents and Children (ALSPAC), lung physiology, pulmonary function tests, cohort study, asthma

FUNDING
ALSPAC receives core funding from the UK Medical Research Council, the Wellcome Trust (Grant ref: 102215/2/13/2) and the University of Bristol. The lung function measures were supported by a grant from the UK Medical Research Council (G0401540).
Running title: Effect of early term birth on respiratory outcomes
Abstract

Background: Early term-born subjects, (37-38 weeks’ gestation), form a large part of the population and have an increased risk of neonatal respiratory morbidity and childhood respiratory symptoms; there is paucity of data on their later lung function. We sought to (a) compare lung function at 8-9 and 14-17 years in early term-born children with full term-born children (39-43 weeks’ gestation); (b) assess the role of caesarean section delivery, and (c) compare respiratory symptoms and diagnosis of asthma.

Methods: Caucasian, singleton, term births from the Avon Longitudinal Study of Parents and Children (n = 14,062) who had lung spirometry at 8-9 (n=5,465) and/or 14-17 (n=3,666) years were classified as early or full term.

Results: At 8-9 years, standardised spirometry measures, although within the normal range, were lower in the early term-born group, (n=911), compared to full term controls (n=4,554). Delivery by caesarean section in general did not influence later spirometry, and the effect of early term birth was not modified by delivery by caesarean section. At 14-17 years, the spirometry measures in the early term group, (n=602), were similar to the full term group (3,064), and the rates of asthma or respiratory symptoms between the two gestation groups were also similar.

Conclusions: Early term-born children had lower lung function values at 8-9 years compared to the full term group, but were similar by 14-17 years of age. Delivery at early term should be avoided due to early and late morbidity.
INTRODUCTION

In 2013, it was recommended that deliveries at 37-38 weeks’ gestation should be defined as early term. Early term-born infants are known to be at an increased risk of neonatal respiratory morbidity. A retrospective cohort study of over 30,000 low risk singleton neonates reported that early term delivery at 37 weeks’ gestation was an independent predictor for composite respiratory morbidity compared with delivery at 39 weeks’ gestation. It has also been reported that early term-born children have increased respiratory symptoms and admissions to hospital for respiratory illnesses during childhood. We have recently confirmed this finding, and have also extended the finding of increased respiratory symptoms in preschool and school aged children. However, there is a paucity of data on the longer term lung function outcomes in early term-born subjects.

Early term-born subjects form a large proportion of the population. In 2012, the UK Office for National Statistics reported that 19% of all live births were early term births. A retrospective study of over 180,000 births at 37 to 41 weeks’ gestation reported early term deliveries accounted for 34% of term births. There were many reasons why early term births occurred; the most common were spontaneous onset of labour (54%), or elective early delivery for maternal or foetal reasons (28%). The study also reported a higher rate of neonatal respiratory morbidity for early term-born babies when compared to full term-born.

The issue of respiratory morbidity in early term births could be confounded by the association of delivery by caesarean section and later respiratory disease. In the Netherlands, a cohort study of elective caesarean sections at term reported more than 50% of elective caesarean sections are performed at <39 weeks’ gestation. A recent meta-analysis suggested that children delivered by caesarean section have an increased risk of asthma (OR 1.16, 95% CI
1.14, 1.29). In addition, a recent review reported that early term-born compared with full term-born infants delivered by caesarean section have an increased risk of neonatal respiratory morbidity. However, we recently showed evidence for independent rather than interactive effects of early term birth and caesarean section delivery for increased respiratory symptoms in childhood.

Whilst late preterm-born subjects are increasingly recognised as being at risk of long term respiratory morbidity, it is unclear if early term-born children have increased respiratory symptoms. We, therefore, (a) compared lung function and respiratory symptoms at 8-9 and 14-17 years in a population-based cohort of children who were born early term (37-38 weeks’ gestation) compared with similar aged children from the same population born at full term (39-43 weeks’ gestation). (b) We also assessed if any effect of being born early term on later lung function was independent of any effect on later lung function of delivery by caesarean section. (c) We compared lung function at both time points in children born at 37-43 weeks’ gestation by caesarean section with children born by vaginal delivery.
MATERIALS AND METHODS

ALSPAC

The study used data from a longitudinal birth cohort study, the Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC recruited 14,541 women during pregnancy and studied these women and the resulting 14,062 surviving offspring. The methodology of the study has been previously well reported. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. For each of the specific hands-on measurements specific informed consent was obtained from each participant.

Gestational age

Calculation of gestational age was reported based on foetal scans, the mother’s last menstrual period (LMP) particularly if the mother was sure of this, or on clinical records. Where the infant was reported to be born preterm or after ≥43 weeks’ gestation, medical records were reviewed by a clinician who assessed the best gestation using all available clinical information. Only Caucasian, singleton births of 37-43 weeks’ gestation with a birth-weight recorded were included. As we only wanted to report data for term babies, we excluded children with gestations of <37 weeks’ (preterm births), and >43 weeks’ gestation which were deemed to be implausible. The children who had spirometry results at either 8-9 or 14-17 years of age and those who had maternal-reported symptom questionnaires at 7.6 and 13.8 years of age were classified into two groups according to gestational age at birth: 37-38 weeks’ (early term), and 39-43 weeks’ (full term controls). The children who had spirometry results at either age were separately classified into two groups based on mode of delivery: caesarean section or vaginal delivery. The children in the caesarean section group
were further classified into two groups according to type of caesarean section: emergency or elective.

**Spirometry measures**

As previously reported spirometry was performed at two time points. Standard deviation scores (z-scores) adjusted for age, sex and height were calculated for forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and forced mid-expiratory flow between 25 and 75% of FVC (FEF₂₅₋₇₅) according to the method by Chinn and Rona as previously reported. Ratios of FEV₁/FVC and FEF₂₅₋₇₅/FVC were calculated from the raw lung function values as markers of airway obstruction and dysanapsis.

**Self-Reported Respiratory Symptoms and Tobacco Smoke Exposure**

Questionnaire data completed at 7.6 years of age reported if the children “ever had asthma diagnosed by a Doctor together with symptoms and/or treatment in the previous 12 months” and at 13.8 years of age if the children “ever had asthma diagnosed by a Doctor”. At 8.6 and 16.5 years of age, it was reported if the children had “suffered wheezing with whistling on chest in past year”. In addition, the questionnaires also collected data on doctor visits for wheezing symptoms, for asthma and asthma medication use in the past year. Tables 4, 5 and 6 show the actual questions asked and who completed each questionnaire.

Regular smoking at age 14 was defined as the usual smoking of at least one cigarette per day or at least six cigarettes per week.

**Bronchial Responsiveness**

As previously described at 8-9 years of age children, unselected for asthma or wheezing,
had a bronchial challenge test with methacholine using the rapid method of Yan et al. 20

**Statistical Analysis**

Birth-weight z-scores were calculated using the LMS Growth program (Medical Research Council, UK). 21

Spirometry values are summarised using the mean, together with 95% confidence intervals. To account for confounders, spirometry data which had been adjusted for age, gender and height, were further adjusted for smoking during pregnancy, social class based on the father’s occupation, and in additional analyses, delivery by caesarean section using general linear modelling. Differences between the early term and full term groups, and the mode of delivery groups were tested using independent samples t-tests. Linear regression was used to investigate the interaction between early term birth and delivery by caesarean section on later lung function at both time points separately for children who had accurate data on mode of delivery and lung function measurements at both time points. The differences between the groups for the ratios FEV$_1$/FVC and FEF$_{25-75}$/FVC were tested using non-parametric bootstrapped methods. Bronchial hyper-responsiveness was compared between the two gestation groups. The geometric mean PD$_{20}$ for the responders to the metacholine challenge in each of the gestation groups, and the geometric mean PD$_{20}$ for all the children who underwent the metacholine challenge in each of the gestation groups were calculated, and an independent samples t-test of the logarithmic PD$_{20}$ values were used to compare the early term group with the full term group. 22 Chi-squared tests were used to compare asthma rates between gestation groups at 7.6 and 13.8 years of age and the questionnaire data at 8.6 and 16.5 years of age. p-values less than 0.05 were considered statistically significant. As a sensitivity analysis, we repeated the analyses for children who had lung function data at both 8-9 and 14-17 years of
age, and completed the five questionnaires on respiratory symptoms. All analyses were performed using PASW 20 (SPSS Inc. Chicago, Illinois, USA).
RESULTS

From 10,696 term singleton Caucasian live births, spirometry data were available from 5,465 (51.1%) children at 8-9 years of age and 3,666 (34.3%) at 14-17 years of age. Tables 1 shows the characteristics of the children in the two gestation groups who had spirometry. Significantly more children in the early term group were delivered by a caesarean section compared with the full term group. As expected children in the early term-born group had a significantly lower birth-weight than the full term-born, although when birth-weight was standardised, the z-scores showed the reverse. The weight at 14-17 years of age was heavier in the early term group but the z-scores corrected for gender and gestation were not different. There were a higher percentage of male children in the early term-born groups compared to the full term-born groups at each of the lung function and questionnaire time points. Relevant data is shown below each table. We previously reported that more children who did not attend for spirometry were from a lower social class and had higher exposure to maternal smoking.12

Association of early term birth and caesarean sections with lung function in later childhood

Spirometry data for the two gestation groups at 8-9 and 14-17 years of age are shown in Table 2. At 8-9 years, all standardised spirometry measures were close to zero but the difference in standardised spirometry measures were significantly lower in the early term group compared with the full term group. The difference in standardised spirometry measures remained significant when the two confounders, maternal smoking in pregnancy and paternal social status were adjusted for. The ratios FEV1/FVC and FEF25-75/FVC were not different between the two gestation groups. At 14-17 years, all standardised spirometry measures and
the ratios were similar between the early term group and the full term groups including after adjustments for confounders.

Table 3 shows the lung function outcomes according to mode of delivery. With exception of FVC at 8-9 years of age, the standardised spirometry measures and ratios were not different between the mode of delivery groups. When the data for the gestation groups was further adjusted for delivery by caesarean section, the results were very similar as shown (Table 2).

We investigated the interaction between early term birth and delivery by caesarean section for children who had accurate mode of delivery data and lung function measures at both time points. Early term birth had a negative effect on later lung function when only early term birth was included in the model, although this only reached significance for FEF25-75 at 8-9 years of age. When delivery by caesarean section and the interaction between caesarean section and early term birth were also included in the model, caesarean section, in general, had a smaller negative effect on later lung function than early term birth. The effect of early term birth was not modified by delivery by caesarean section except for FEV1 at 14-17 years of age (Table 3). We investigated the effect of elective caesarean sections (n=213 at 8-9 years and n=133 at 14-17 years of age respectively) and emergency caesarean sections (n=197 at 8-9 years and n=142 at 14 -17 years of age respectively) on lung function. In general the standardised spirometry measures were not different between the type of caesarean section groups and the vaginal delivery group (data not shown).

**Asthma and questionnaire data**

Rates of asthma at 7.6 and 13.8 years of age are shown in Table 5. Asthma in the previous year at 7.6 years of age was reported by 15.0% in the early term group and 13.6% in the full
term group; \( p = 0.235 \). The rates of asthma ever at 13.8 years of age were also similar 23.7\% and 22.3\% in the early and full term groups respectively; \( p = 0.332 \).

Respiratory questionnaire data at 8.6 and 16.5 years of age are shown in Tables 5 and 6. In general there were no differences between the two groups except for marginal differences at 8.6 years of age - more children in the full term group than in the early term group reported that the child had asthma in the past year and saw a doctor. No significant differences were noted between the respiratory symptoms reported in the early term and full term group at 16.5 years of age.

Of the children who had any lung spirometry, 84 (1.4\%) children reported regular smoking at 14 years of age with 13 (1.3\%) in the early term-born group and 71 (1.4\%) children in the full term-born group.

**Sensitivity analysis**

When the sensitivity analyses was performed for only children who had lung function at both ages, the numbers decreased markedly to 262 from 911 children who had lung spirometry at 8-9 years of age for the early term group and to 1224 children, from the 4554 children, for the term group. Nevertheless, early term birth continued to have a negative effect although not significantly on later lung function particularly at 8-9 years of age before and after adjustment for confounders. However, possibly due to the decreased numbers, the differences when the early term-born group was compared to the full term-born group were no longer significant at 8-9 years of age. The results for questionnaire data remained insignificant (data not shown).
Bronchial responsiveness

617/911 (67.7%) of the early term group and 3209/4554 (70.5%) of the full term group underwent the metacholine challenge. 14.7% and 15.6% of the early term and full term group respectively responded to the metacholine challenge. The geometric mean PD$_{20}$ in responders was 1.84µmol (95% CI 1.47, 2.30) and 1.74µmol (95% CI 1.57, 1.92) in the early term and full term groups respectively. The geometric mean PD$_{20}$ for the whole population who underwent the challenge was 9.20µmol (95% CI 8.65, 9.79) and 8.97µmol (95% CI 8.72, 9.23) in the early term and full term groups respectively. No significant differences were noted between the two gestation groups for the geometric mean PD$_{20}$ in either responders or the whole study population.
DISCUSSION

Although the mean z-scores for FEV\textsubscript{1}, FVC AND FEF\textsubscript{25-75} in the early term group were close to zero, they were significantly different to the mean z-scores for the full term-born children at 8-9 years of age, but they were similar between the groups by 14-17 years of age. Whether this is due to selection bias or the effects are true will need replication elsewhere. The differences remained after adjustments for confounders, including delivery by caesarean section, but did not appear to be associated with increased respiratory symptoms. However, it is possible that these small differences may become clinically significant in later life and that a higher proportion of the early term-born group may fall below a “critical threshold” in later life; which may lead to them developing respiratory symptoms in later life. Barker et al. showed a relationship between birth-weight and later mortality from COPD; but the differences in lung function were small at 59-70 years.\textsuperscript{23} It was interesting to note that the differences that were present at 8-9 years of age in the early term-born group largely disappeared by 14-17 years of age. The data suggest that “catch-up” growth as recently shown by using hyperpolarised \textsuperscript{3}He MRI scans perhaps during puberty may occur in those born at early term.\textsuperscript{24} There were on the whole, no differences in respiratory symptoms, rates of asthma or bronchial hyper-responsiveness between the early term-born and full term-born groups at both time points studied.

It is recognised that early term-born infants are at an increased risk of respiratory morbidity in the neonatal period.\textsuperscript{25} The longer term lung function outcomes of early term-born children have not been studied in any detail previously; although respiratory symptoms and rates of asthma in early term-born children have been reported.\textsuperscript{4,6,26} In contrast to our results, Boyle et al reported an adjusted odds ratio of 1.1 for wheezing or whistling in the chest at 3 years
for children born early term compared with children born at 39-41 weeks’ gestation. At 5 years, the adjusted odds ratio was 1.2 for wheezing or whistling in the chest in the previous 12 months for children born early term when compared with those born at 39-41 weeks’ gestation. In addition, the adjusted odds ratio for use of prescribed asthma drugs at 5 years was 1.4 for children born early term compared to those born at 39-41 weeks’ gestation. In support of early term-born children having worse respiratory health than their full term-born counterparts, we have recently reported that early term birth is associated with increased respiratory symptoms throughout childhood, increased neonatal admissions, and hospital admissions in first year of life, inhalers and antibiotic use. Unlike our recent study, we did not note greater symptoms in the current study in the early term-born group. This may be due to a cohort from a different era for whom the indications for caesarean section, which often result in early term births, were different especially as rates have increased markedly in recent years. Nonetheless, several more recent studies do show increased symptoms in early term-born children. Harju et al also reported an increased adjusted odds ratio for asthma in early term-born children of 1.2 compared with children born at 39-40 weeks’ gestation. None thus far have reported lung function.

The current rate of delivery by caesarean section in the UK is much greater than it was in 1990-1992 when the ALSPAC cohort was delivered. In 2013 -2014, the overall rate of delivery by caesarean section delivery was 26.2%. It has been reported that delivery by caesarean section is linked to an increased risk of asthma in later life. However our study shows no convincing evidence that the effect of early term birth on later lung function is modified by caesarean section delivery. One large study reported early term-born children had an increased risk of hospitalisation for asthma compared with children born at 39-41 weeks’ gestation; however, the associations were similar in children delivered by caesarean
Our recent study appears to suggest that respiratory symptoms in early term-born children in childhood were independent of caesarean section. These results are in line with a previous study using the ALSPAC cohort concluded that development of asthma or wheezing was not linked to delivery by caesarean section in both term- and preterm-born children.

The mechanisms responsible for the lung function deficits observed in early term children at 8–9 years of age are not known. It is possible that they may result from fractionally earlier delivery and delivery at a slightly earlier stage of lung development, or that lung function deficits arise from increased neonatal respiratory morbidity in these children e.g. respiratory distress syndrome. It is recognised that delivery by caesarean section increases respiratory symptoms in later life; but our data and the data we have previously published questions if delivery by caesarean section is an independent risk factor for future development of wheeze. Early term-born children born by both vaginal delivery and caesarean section both had reduced lung function in later life in this study. Whilst many have focussed on the hygiene hypothesis, these data taken together suggest alternative mechanisms such as consequences of early neonatal respiratory distress which need further study.

A limitation of using data from ALSPAC is that the data were not collected to address this specific hypothesis; however this may be a strength as it will reduce biased responses. The loss to follow up, as seen in all cohort studies, is a limitation as is the resulting potential attrition bias. However, the strength of this study is that it uses data from a large unselected population-based cohort which contains longitudinal data from of large number of early term-born and full term-born children; and spirometry was measured using the same methods at the two time points. A further limitation is that the respiratory questionnaires were conducted
at time points different to the lung spirometry; and the children included in the respiratory questionnaires may differ to the ones who had lung spirometry results. When only children who had lung function at both ages and questionnaire data for all time-points, a negative but not significant effect on later lung function particularly at 8-9 years of age was noted. In addition, gestation might be misclassified as routine ultrasound scanning was not available for all women at the time. However, the best known gestation was recorded by all available methods at the time focusing especially on preterm and post term-born infants. Furthermore, we excluded those with post term gestation of ≥43 weeks’ gestation but a small numbers may be misclassified into early term or term groups although the results are unlikely to be affected. The ALSPAC cohort is thought to be fairly similar to the population of the United Kingdom hence results are likely to be generalizable to the population of the UK. Other confounders such as maternal health, pregnancy related conditions such as pre-eclampsia or drugs such as antenatal maternal corticosteroids are likely to be important but very few of the women reported pre-eclampsia or received antenatal corticosteroids thus was not included in the analyses.

CONCLUSION
There is a paucity of data on the longer term lung function outcomes of early term-born children. Our data showed deficits in lung function for the early term-born children compared to the full term-born children at 8-9 years of age but not 14-17 years of age. In general, the respiratory symptoms and increased rate of asthma seen in other studies was not reported here and symptoms were not increased. Whilst the hygiene hypothesis has received attention for increased wheeze in childhood after caesarean sections, other mechanism which may be independent of the hypothesis may also be important including the relative immaturity of the infants, or alterations in the microbial milieu that the infants are colonised with or
consequences of early neonatal disease.
ACKNOWLEDGEMENTS

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. This publication is the work of the authors and Professor Sailesh Kotecha will serve as guarantors for the contents of this paper.

COMPETING INTERESTS

Prof. Sailesh Kotecha reports grants from Welsh Government, other from VoluSense, grants from EU FP7, grants from MRC, outside the submitted work. Prof A. John. Henderson reports grants from Wellcome Trust, grants from Medical Research Council, during the conduct of the study.
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