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Relationship between birth weight, maternal smoking during pregnancy and childhood and adolescent lung function: A path analysis

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ABSTRACT

Background: Low birth weight and gestational maternal smoking have been linked with reduced lung function in children in many cross sectional studies. However, these associations have not yet been assessed with repeated measurements of lung function. Our aim was to investigate the effects of birth weight, gestational age, and gestational maternal smoking on lung function in children at age 10 and 18 years.

Methods: In the Isle of Wight birth cohort spirometry was performed at age 10 and 18 years. Information on birth weight and gestational age were obtained from hospital records. Mothers were asked about smoking during pregnancy. We employed linear mixed models to estimate the effect of these risk factors on repeated measurements of lung function. We considered maternal asthma, sex, neonatal intensive care unit admission, height, socio-economic status, personal smoking in participants at age 18, body mass index and environmental tobacco smoke exposure as potential confounders. Finally, we used path analysis to determine links between birth weight, gestational age and gestational maternal smoking on lung function at age 10 and 18 years.

Results: Linear mixed models showed that with every 1 kg increase in birth weight, Forced expiratory volume in one second (FEV_1) increased by 42.6 ± 17.2 mL and Forced expiratory flow between 25% and 75% (FEF_{25-75}) of Forced vital capacity (FVC) increased by 95.5 ± 41.2 mL at age 18 years after adjusting for potential confounders. Path analysis suggested that birth weight had positive direct effects on FEV_1 and FEF_{25-75} and positive indirect effect on FVC at 10 years which were carried forward to 18 years. Additionally, results also suggested a positive association between gestational age and FEV_1, FVC and FEF_{25-75} at ages 10 and 18 years and an inverse association between gestational smoke exposure and FEV_1/FVC ratio and FEF_{25-75} at age 18 years.

Conclusions: Higher birth weight and gestational age were associated with higher FEV_1, FVC and FEF_{25-75} and maternal smoking during pregnancy was associated with reduced FEV_1/FVC ratio and FEF_{25-75}. The use of path analysis can improve our understanding of underlying "causal" pathways among different prenatal and childhood factors that affect lung function in both pre-adolescent and adolescent periods.

1. Introduction

The 'Barker hypothesis' also known as 'fetal origins of adult disease' hypothesis, states that adverse exposures encountered during intrauterine life can result in permanent changes in physiology which may result in increased risk of chronic diseases in adulthood [1]. Barker et al. showed that, fetal and infant growths

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are associated with lung function in adults and low birth weight (LBW) may increase the risk of death from chronic obstructive lung disease [2]. Other studies have also shown that LBW and very low birth weight (VLBW) are associated with reduced lung function in children [3–7]. Two more studies have found a positive relationship between continuous birth weight measures and lung function in children [8,9]. In adults, the findings are mixed, some studies reported a significant positive linear trend between birth weight and lung function [10–13], while other studies found no association [14].

The process of lung development begins in the intrauterine period and continues well into late adolescence/early adulthood. Therefore, intrauterine exposures affecting lung development during fetal life, for example maternal smoking, may have a long term negative impact on lung function. Additionally, maternal smoking during pregnancy is known to result in pre-term births and LBW in full term babies [15,16]. Thus, maternal smoking during pregnancy, gestational age and birth weight are correlated and birth weight may be in the pathway between *in-utero* exposure to maternal smoking and lung function. However, there is disagreement on whether maternal smoking during pregnancy has independent effect on reduction of lung function in childhood [17–19]. Previous studies while investigating association between birth weight and lung function have adjusted for the effect of maternal smoking during pregnancy without addressing the fact that birth weight may be an intervening variable. Similarly, height which is a significant determinant of lung function may also act as an intervening variable in the path between birth weight and lung function as many pediatric studies have shown a positive association between birth weight and growth of height during childhood [20,21].

Lung function during childhood and adolescent periods is determined by complex relationships between several factors that need to be taken into account simultaneously. However, adjusting for intervening variables as confounders not only distorts the causal pathway but also leads to an over-adjustment bias [22]. The inconsistent results in association between birth weight and lung function in the above mentioned studies may be attributed to the use of traditional regression analyses, which do not take into consideration the directional or non-directional relationships between various observed factors. To elucidate these complex relationships, use of path analysis provides a novel approach. A variable representing the response in one equation can act as a risk factor in another equation, thus allowing the inclusion of intervening or mediating variables in the model. Finally, simultaneously solving multiple linear regression equations generates direct, indirect and total effects of each variable on the outcome, which can be used to develop a causal path diagram.

To gain better understanding of the relationship between birth weight, maternal smoking, and lung function in children at age 10 and 18 years, we analyzed data from the Isle of Wight (IOW) birth cohort. We explored these associations first by using linear regression, followed by linear mixed models and path analysis in which we assessed complex relationships between different prenatal and childhood factors that may affect the association between birth weight and lung function.

2. Materials and methods

2.1. Study population

Between January 1989 and February 1990, 1536 mothers/child pairs were contacted to be enrolled in the IOW birth cohort. After obtaining informed written consent 1456 were enrolled and available for follow-up at 1, 2, 4, 10 and 18 years of age. Among them, 1121 children were tested for spirometry either at 10 ($n = 981$) or 18 years of age ($n = 838$) or both ($n = 698$) The IOW cohort is described in detail elsewhere [23–25].

2.2. Birth weight and other measurements

Information on birth weight, gestational age, and admission to neonatal intensive care unit (NICU) were obtained from the hospital records. Information on maternal smoking during gestation, sex of the child, and maternal history of asthma was ascertained after delivery. We considered maternal smoking during gestation, maternal history of asthma, sex, admission to NICU, height, socioeconomic status (SES), personal smoking in children at age 18, body mass index (BMI) and environmental tobacco smoke (ETS) exposure at age 10 and 18 as potential confounders or intervening variables. Information on the SES was based on the following three variables: (a) the British socioeconomic classes (1–6) derived from parental occupation reported at birth; (b) the number of children in the index child's bedroom (collected at age 4 years); and (c) family income at age 10 years [25]. Height and weight were measured before spirometric tests at age 10 and 18 years; BMI was calculated. To address the differential growth pattern in height in boys and girls we considered an interaction term between height and sex. Exposure to ETS at age 10 and 18 was inquired from questions of “any smoking in the household”. Active smoking at age 18 years was ascertained from the study participants at age 18.

2.3. Lung function

Lung function tests were conducted at 10 and 18 years of age. Forced vital capacity (FVC), Forced expiratory volume in one second (FEV_1), Forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}) and Peak expiratory flow rate (PEFR) were measured using a Koko Spirometer and software with a portable desktop device (both PDS Instrumentation, Louisville, KY, USA). Spirometry was performed and evaluated according to the American Thoracic Society (ATS) criteria. Children were required to be free of respiratory infection for two weeks and not to be taking any oral corticosteroids and were advised to abstain from any β-agonist medication for six hours and from caffeine intake for at least four hours [23].

2.4. Statistical analysis

Firstly, to determine effects of birth weight and maternal smoking during pregnancy on lung function at cross-sectional level we used standard linear regression technique separately at ages 10 and 18 years. Next, we used linear mixed models for repeated measurements on cohort of children who were tested for lung function either at age 10 or18 years or both. Unstructured covariance structure matrix was selected based on lowest Akaike information criteria and the Bayesian Schwarz information criterion after considering unstructured, compound symmetry and autoregressive covariance structure matrices. All models were adjusted for above mentioned confounders. The models assessing the relationship between maternal smoking *in-utero* and lung function and gestational age and lung function were not adjusted for birth weight. We selected the confounders that changed the estimates of main exposures (birth weight, exposure to *in-utero* maternal smoking and gestational age) by 10%. We also included an interaction term between sex and height since the relationship between height and lung function varies by sex [26]. To control for type-I error due to multiple comparisons the significance level was set at alpha = 0.025 whenever interaction term between height and sex was included in the model. Otherwise significance level of alpha = 0.05 was maintained for rest of the models.