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Prenatal, early-life and childhood exposure to air pollution and lung function: the ALSPAC cohort

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AUTHOR'S CONTRIBUTION

P.E. and A.J.H. conceived the study idea and design. J.G. and D.F. provided input on exposure modelling. M.B. and R.G. provided input on the methodology for analysing the data. Y.C. and A.L.H. did the main data analyses and wrote the manuscript. M.Z. provided input on the profile regression analysis. All authors (i) provided substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, (ii) revised the manuscript for important intellectual content, (iii) approved the final version, and (iv) agreed to be accountable for all aspects of the work. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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SHORT RUNNING TITLE

Air pollution and children lung function

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1.17 Epidemiology (Pediatric): Risk Factors

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Few studies to date in children aged between 4-11 years have investigated the role of air pollution in each trimester on lung function and these had sample sizes ranging from 171 to 788 individuals. Some studies suggested that exposure to traffic-related air pollutants, particularly during the second trimester, was associated with reduced lung function, although correlations between these trimester-specific exposures were high. Evidence was inconsistent regarding the relative importance of early-life or more recent air pollution exposure on childhood lung function levels. Also, some studies suggested that the negative associations between early life air pollution exposure and childhood lung function became absent or diminished by adolescence.

What This Study Adds to the Field

This is the largest study to investigate source-specific particulates by each pregnancy trimester as well as infancy and childhood to identify potential susceptibility periods during lung development and growth. We found that particulate exposures in each time period in pregnancy and early life were associated with reduced lung function at age 8 years. The third trimester

may be a potential susceptible period for PM_{10} from all sources but for PM_{10} from road traffic, no especially susceptible periods could be identified.

ONLINE DATA SUPPLEMENT

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org .

WORD COUNT

3,636 words

1

ABSTRACT

Rationale: Exposure to air pollution during intrauterine development and through childhood may have lasting effects on respiratory health.

Objectives: To investigate lung function at ages 8 and 15 years in relation to air pollution exposures during pregnancy, infancy and childhood in a UK population-based birth cohort.

Methods: Individual exposures to source-specific particulate matter with diameter ≤10μm (PM_{10}) during each trimester, 0-6 months, 7-12 months (1990-1993) and up to age 15 years (1991-2008) were examined in relation to %predicted Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) at ages 8(N=5,276) and 15(N=3,446) years, usinglinear regression models adjusted for potential confounders. A profile regression model was used to identify sensitive time periods.

Measurements and Main Results: We did not find clear evidence for a sensitive exposure period for PM_{10} from road-traffic: at age 8 years, 1μg/m^3 higher exposure during the first trimester was associated with lower %predicted of FEV_1(-0.826, 95%CI:-1.357 to -0.296) and FVC(-0.817, 95%CI:-1.357 to -0.276), but similar associations were seen for exposures for other trimesters, 0-6 months, 7-12 months, and 0-7 years. Associations were stronger among boys, children whose mother had a lower education level or smoked during pregnancy. For PM_{10} from all sources, the third trimester was associated with lower %predicted of FVC (-1.312, 95%CI: -2.100 to -0.525). At age 15 years, no adverse associations were seen with lung function.

Conclusions: Exposure to road-traffic PM_{10} during pregnancy may result in small but significant reductions in lung function at age 8 years.

Word count: 246 words

Key words: ALSPAC, children, traffic, air pollution, respiratory health

INTRODUCTION

There is a growing awareness that early-life exposure to air pollution potentially has detrimental effects on the future respiratory health of both children and adults, with impacts on lung function trajectories throughout life(1, 2). In the developing fetus, the bronchial tree is formed by 16 weeks of gestation while alveolarization begins at approximately 28 weeks, and by age two years almost the final adult number of alveoli have been formed, although the development process could continue throughout adolescence to early adulthood(3). It is biologically plausible that exposure to air pollution in early life could lead to impaired lung function growth and reduced maximal levels of forced expiratory volume in one second (FEV_1) attained in early adulthood, which is associated with long term respiratory morbidity even with physiological levels of subsequent decline(4).

Limited information still exists about whether exposure to air pollution during periods of rapid pulmonary development in pregnancy and infancy is independently related to long-term lung function compared with exposures throughout whole life. Most previous studies have reported negative associations between air pollution exposures after birth at various life stages and childhood lung function(5-19), although which time period of exposure (early-life vs. most recent) has the strongest associations is debated. Notably, relatively few studies(20-24) to date, have specifically investigated prenatal air pollution exposures, also with mixed findings in terms of susceptibility periods.

To address these gaps in knowledge, we used a large, population-based birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort(25, 26), to investigate lung function at ages 8 and 15 years in relation to modelled source-specific and all-sources air pollution exposures at residential addresses during each trimester of pregnancy, whole pregnancy, early infancy, late infancy and during childhood. Some of the results of this study

have been previously presented at the International Society of Environmental Epidemiology 2018 annual meeting(27).

METHODS

Study participants

Pregnant women residing in the former administrative county of Avon in south-west England, whose estimated delivery date fell between 1 April 1991 and 31 December 1992 were recruited before birth, resulting in a cohort of 14,541 pregnancies(25, 26) with 13,963 children eligible for this study(Figure S1). The cohort has been followed with longitudinal assessment of exposures and outcomes from pregnancy to adulthood via questionnaires and clinic visits(25). Ethical approval was obtained from the ALSPAC Ethics and Law Committee and Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool: http://www.bristol.ac.uk/alspac/researchers/our-data/.

Data sources and measurements

Lung function was measured by spirometry (Vitalograph 2120; Vitalograph, Maids Moreton, United Kingdom) at age 8 (median 8.6, range 7.5 to 10.5 years) and 15 years (median 15.4, range 14.2 to 17.7 years) according to American Thoracic Society standards(28). Both pre- and post-bronchodilation measures at age 15 years were obtained whilst at age 8 years only pre-bronchodilation measures were available. At both ages, children who had oral steroids or chest infection in the past three weeks, used either short-acting bronchodilator in the past six hours, or long-acting bronchodilator in the 24 hours before the lung function tests, were excluded

from the analysis (Figure S1). Using measures of post-bronchodilation at age 15 years and pre-bronchodilation at age 8 years, we derived %predicted values of FEV_1, Forced Vital Capacity (FVC), and FEV_1/FVC ratio for each age using the Global Lung Function Initiative (GLI) equations (https://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools.aspx, accessed February 2020).We also calculated rate of lung function growth from age 8 to 15 years (pre-bronchodilation measures at 15 years - pre-bronchodilation measures at 8 years/time of follow-up in years)(31).

Sex and gestational age categorised as preterm (<37 weeks) and non-preterm (≥37 weeks) were obtained from birth records. Questionnaires completed by mothers provided information on: maternal education level (low: educated at school to 16 years or lower vs. high: educated to above 16 years); maternal smoking in the first three months of pregnancy (yes/no); home ownership (rented vs. owned/mortgaged) and presence of damp and mould in the home (yes/no) when the study child was 8 months old; study child ever exposed to passive smoking up to age six and half years (yes/no); study child ever had breastfeeding (yes/no). Current asthma was defined at ages 8 and 15 years as reported doctor's diagnosis of asthma and reported wheezing, or use of asthma medication in the previous 12 months.

A full residential address history was constructed through the Algorithm for Generating Address-history and Exposures (ALGAE; https://smallareahealthstatisticsunit.github.io/algae/index.html, accessed in February 2020) and was geocoded for each trimester (T1, T2, T3), early infancy (0-6 months), late infancy (7-12 months), and every year up to age 15 years(32). For geocoding, individuals for each exposure period must have had valid addresses for at least 90% of days in trimesters and infancy, and at least 75% of days within each year of life up to age 15 years, thus number of individuals retained for each exposure period was different. We used dispersion modelling to

estimate residential air pollution exposures to particulate matter (PM) from different sources during each trimester and infancy (1990-1993) through childhood to adolescence up to age 15 years (1991-2008), taking account of residential mobility(33). Modelled daily estimates of PM with an aerodynamic diameter ≤10μm (PM_{10}) from local major road traffic (PM_{10}_road, hereafter) were based on information on traffic flows, composition, speed, tail-pipe and non-tailpipe emission rates, road width, building heights for street canyons and meteorological variables; whilst PM_{10} emissions on a 1x1km grid from other local combined sources such as industrial, domestic or minor roads (PM_{10}_other, hereafter) were obtained by subtracting summed emission rates from main roads from total PM_{10} emission using the National Atmospheric Emissions Inventory (http://naei.beis.gov.uk/data/data-selector, accessed February 2020); and total PM_{10} (PM_{10}_total, hereafter) was a combination of PM_{10}_road, PM_{10}_other, anthropogenic sources outside the study area and secondary formation of PM from UK and western Europe from the Met. Office's NAME model(34), and a constant to represent local non-anthropogenic sources (e.g. wind-blown soil, dust). Each source-specific PM_{10} estimate was averaged for each trimester, whole pregnancy and infancy period (T1, T2, T3, WP, 0-6 months, 7-12 months) for each study child. In addition, for each child annual average source-specific PM_{10} concentrations (PM_{10}_road; PM_{10}_other) and total sources (PM_{10}_road, PM_{10}_other, anthropogenic, and non-anthropogenic background concentrations) were estimated every year after birth up to age 15 years.

Statistical analyses

Average daily PM_{10} exposures for each trimester, whole pregnancy, 0-6 months, 7-12 months and annual PM_{10} exposures for ages 0-7, 8-15 and 0-15 years were analysed as continuous measures. Linear regression models were fitted to assess associations with %predicted of lung function (FEV_1, FVC, FEV_1/FVC) at both ages 8 and 15 years. Effect estimates were presented

as per 10μg/m^3 increment in PM_{10}_total exposure and per 1μg/m^3 increment in PM_{10}_road and PM_{10}_other. All analyses were undertaken using Stata v12.1 (College Station, Texas, USA).

Main model was adjusted *a priori* for sex, gestational age, maternal education, home ownership, maternal smoking during pregnancy, passive smoking in childhood, damp and mould presence at home, and season of clinic visit. To correct for multiple testing, we used the Simes procedure and generated q-values using the 'qqvalue' package in Stata.

Sensitivity analyses were conducted by adding each of the following variables into the main model: current asthma, current body mass index, ever had breastfeeding and small for gestational age (SGA) (i.e. birth weight <10^{th} percentile for gestational age vs. 10^{th}+ percentile).

Potential effect modifications by child's sex, maternal education and maternal smoking were examined by adding into the models an interaction term between PM_{10} exposure and each of these variables.

Missing data of PM_{10} exposures, covariates and outcomes in the main model were imputed by using multiple imputations. Ten new datasets were created by means of imputation, achieving a complete sample size of 13,963 for each dataset. All datasets were analysed separately, after which results were combined using Rubin's rule(35). Complete-case analysis was conducted in which children were only included if information on PM_{10} exposures, covariates and outcomes at both ages 8 and 15 years were all available.

Spearman correlations between PM_{10} for different time periods were calculated. To investigate the independent effects of PM_{10}_total exposure in each time period on childhood lung function, exposures from different time periods (i.e. trimesters and infancy; trimesters and childhood) were mutually adjusted in the main model, for which potential multicollinearity was assessed by the variance inflation factor (VIF). As high correlations were seen between PM_{10}_road for

different time periods, a Bayesian profile regression model (supplementary text) was fitted(36) via the R package PReMiuM(37), which enables assessment between potentially collinear variables and an outcome through cluster membership.

Lung function growth rates (litre/year) from ages 8 to 15 years in relation to air pollution exposure were examined using linear regression by additionally adjusting age and height at 15 years in the main model.

RESULTS

Among the 13,963 children, %predicted of lung function were calculated for 5,276 and 3,446 children at age 8 and 15 years respectively(Table1). Mean PM_{10}_total exposures were 33.45 $\mu g/m^3$ in the first trimester and declined in each subsequent period to 30.96 $\mu g/m^3$ by 7-12 months of age (Table 2). The annual average PM_{10}_total exposures for 0-7 years and 8-15 years was 32.99 $\mu g/m^3$ and 22.98 $\mu g/m^3$ respectively. Average PM exposure in each time period by child's sex, maternal education and maternal smoking is presented in Table S1.

Spearman correlations between PM_{10}_road for different time periods were highly correlated(TableS2.1), as also seen for PM_{10}_other(TableS2.2). In contrast, correlations between PM_{10}_total across trimesters, 0-6 months and 7-12 months were low to moderate (ranging from -0.16 to 0.22 except between first trimester and 0-6 months of age (r=0.44) and between second trimester and 7-12 months (r=0.72))(TableS2.3). For the same period, correlations between each source of PM_{10} exposure ranged from 0.48 to 0.96(TableS3).

For PM_{10}_road, each 1$\mu g/m^3$ higher exposure during the first trimester was associated with lower %predicted of FEV_1 (-0.826, 95%CI: -1.357 to -0.296)(Figure1a) and of FVC (-0.817, 95%CI: -1.357 to -0.276)(Figure1b) at age 8 years. Significant negative associations of similar effect size were also seen for the other time periods. In contrast, at age 15 years, all associations

were consistently positive but non-significant except for the first and second trimester and the whole pregnancy, for example, for the whole pregnancy, %predicted of FEV_1 and FVC was higher by 1.317 (95%CI: 0.377 to 2.256) and 1.166 (95%CI: 0.269 to 2.063) respectively. No associations with FEV_1/FVC ratio at either age were seen(Figure1c).

When analyses were restricted to the 1,501 participants with lung function measurements at both ages 8 and 15 years, directions of the associations between PM_{10} exposures and lung function measures at both ages were generally in line with the main analyses, although the effect sizes were much smaller and most associations were non-significant as expected given the smaller sample(Table S4).

The profile regression model for analyses of PM_{10}_road at age 8 years revealed a 'best' partition made of three clusters of participants. The first cluster was characterised by children (n=41) having consistently high exposure to PM_{10}_road throughout the *in-utero* and early-life period, whilst the third cluster was characterised by children (n=3607) having low exposure for the same period, and the exposure profile for the second cluster (n=566) was somewhat in between. Overall, while the second and third cluster did not show substantial differences in the mean values of lung function outcomes, the first cluster was characterised by having lower mean values of FEV_1 (Figure S2) or FVC (Figure S3), although the uncertainty was large because only a small number of participants were included in this cluster. At age 15 years, there was no clear association with either lung function outcome.

For PM_{10}_other, directions of associations at both ages were similar to those of PM_{10}_road, although the effect sizes were smaller and most significant associations did not persist after multiple test correction(FigureS4 a-c).

For PM_{10}_total, associations with both %predicted of FEV_1 and FVC at age 8 years were all negative but with varied strength across time periods. Exposure during the second trimester, whole pregnancy, 7-12 months and 0-7 years was significantly associated with lower % predicted of FEV_1(Figure2a) while significant negative associations were observed for %predicted of FVC in relation to third trimester, whole pregnancy and 7-12 months exposure (Figure2b). The negative association with FVC observed at the third trimester persisted in models mutually adjusted for exposures in other trimesters and infancy periods(TableS5) while multicollinearity was not detected (VIF<10). A significant positive association (0.641, 95%CI: 0.168 to 1.113) in the third trimester was seen for %predicted of FEV_1/FVC ratio at age 8 years(Figure2c), which persisted in models mutually adjusted for exposures in all other periods (TableS5).

At age 15 years, there were significant positive associations between the first trimester exposure and %predicted of FEV_1 or FVC, and between the third trimester exposure and %predicted of FEV_1/FVC ratio, although none of these persisted after multiple test corrections.

At age 8 years, for the associations between PM_{10}_road and %predicted of FVC at all time-periods, negative associations were larger among boys, children whose mother had a lower education level or smoked during pregnancy(Figure3). Similar patterns were also observed for PM_{10}_total(FigureS5).

Sensitivity analyses and analyses using imputed datasets (TableS6.1 & S6.2) did not materially change the main findings. Most associations between air pollution exposure of different periods and lung function growth from age 8 to 15 years were non-significant, except that positive associations were found between PM_{10} exposure of each source during the first trimester and FEV_1 growth(Table S7).

DISCUSSION

In this large cohort followed from antenatal period to age 15+ years, PM_{10} exposures during each pregnancy trimester, infancy and childhood were modelled specifically for road traffic and non-road traffic sources. We found that road-traffic PM_{10} appears to be particularly harmful for mid-childhood lung function. Specific susceptibility time periods in pregnancy and early life were not identified, possibly because exposures to road-traffic PM_{10} were highly correlated across time periods. Associations were larger among boys, children whose mother had a lower education level or who smoked during pregnancy. Associations with total PM_{10} (i.e. from all sources) were less consistent, but pointed to susceptibility periods during the third trimester in relation to lower FVC levels in mid-childhood. However, these negative associations were not observed at age 15 years.

The observed reduction in our study of 0.8% of predicted lung function levels in relation to early-life road-traffic PM_{10} exposure equates to an average decrement of about 14mL FEV_1 and 16mL FVC loss at age 8 years. The deficits, although small for individuals, may unfavourably shift the distribution of average lung function in the population (i.e. numbers of individuals with lower lung function will increase) and this may have long-term implications for lung health(1).

It is difficult to make direct comparisons with the previous studies due to different exposure assessments (e.g. nitrogen dioxide (NO_2) or PM with an aerodynamic diameter $\leq$2.5μm($PM_{2.5}$)), small numbers and different characteristics of the study children (e.g. asthmatics, pre-schooler). $PM_{2.5}$ estimates were not modelled in our study as $PM_{2.5}$ monitoring data only became available from 2008 in Bristol and the surrounding areas(33). Nevertheless, our modelled estimates of PM_{10}_road should be qualitatively comparable to NO_2, NO_X or $PM_{2.5}$, as all are likely to be primarily derived from road traffic sources.

The negative association of PM_{10} derived from road traffic on mid-childhood lung function in our study is consistent with results of previous studies that investigated trimester-specific or prenatal exposures to NO_2 or $PM_{2.5}$. In the Spanish INMA birth cohort of 620 pre-school children age 4.5 years an IQR higher exposure in the second trimester to Land Use Regression (LUR)-derived NO_2 was significantly associated with a 28 ml and 33 ml reduction of FEV_1 and FVC respectively(22). Similarly, an earlier study in California of 232 asthmatic children age 6-11 years reported that FEV_1 and FVC was reduced by 1.2% and 7.1% for each IQR higher second trimester exposure to NO_2, assigned from the nearest monitoring station(21). Whilst these two studies pointed to susceptibility periods during the second trimester, another study (n=171) from Boston, USA found that prenatal exposure to modelled $PM_{2.5}$ in late pregnancy (≥35 weeks gestation) was significantly associated with impaired lung function at age seven years, particularly among boys(24). More recently, the PARIS cohort of 788 children with an average age of 8.5 years did not report such significant negative associations with either FEV_1 or FVC in relation to monitoring-based nitrogen oxides (NOx) exposures in each pregnancy trimester(23).

Unlike previous studies(21, 22, 24), we did not observe an effect from PM_{10}_road limited only to the second trimester or late pregnancy but, given the very high correlations across time periods in these other studies (an issue also encountered in our study for PM_{10}_road), it is difficult to be certain of a critical time window. We did not identify a specific sensitive trimester in relation to PM_{10}_road in the profile regression, but found lower mean FEV_1 and FVC in children with consistently high exposure to PM_{10}_road throughout the in-utero and early life period. Given that our and the other studies discussed above do not consistently identify a pregnancy trimester or early life period particularly susceptible to effects of road traffic air pollution on the developing lung (as measured by lung function), there may not be a

truly trimester specific effect. The public health implications of this are that reduction of road traffic air pollution exposure is important throughout pregnancy and early childhood.

Our findings are also consistent with results of the Swedish BAMSE cohort (2,278 children)(15) and the GINIplus and LISAplus cohorts in Germany (2,266 children)(17) which reported negative associations with air pollution exposures in infancy and lung function at age 8 years, but no significant or even positive associations at 15 years. Two other studies however did not find associations between exposures at birth or first year of life and lung function levels at 6-11 years(7, 12), partly due to uncertainty in modelling historical exposures or a lack of power. Our findings complement those from the Southern California Children's Health Study, which observed that children living closer to a freeway had significant deficits in lung function growth from 10 to 18 years, based on a 'within-community' analysis(5). Recently, the PIAMA birth cohort reported that higher exposure to PM_{10}, $PM_{2.5}$ or NO_2 at birth and age four years was significantly associated with reduced growth in FEV_1 but not FVC from age 8 to 16 years(19). We however did not replicate this finding in the longitudinal analysis using lung function at both ages 8 and 15 years.

As with a previous study(12), effect sizes of air pollutants on both FEV_1 and FVC were similar in our study, indicating that traffic-related air pollution exposure during pregnancy may potentially result in a restrictive pattern of lung function in mid-childhood, but not necessarily predispose children for chronic airflow obstruction.

We found that PM_{10} exposure from all sources, in particular during the third trimester, was negatively associated with FVC at age 8 years. During late fetal life and infancy, the developing lungs undergo structural and functional growth, mainly in formation of small airways which range from terminal bronchioles to alveolar sac(38). It is plausible that during this period exposure to particulate air pollution, associated with oxidative stress and pro-inflammatory

activities, may have impact on development of small airways such as slower growth and/or closure(12), which may lead to a fall in FVC in childhood.

However, as decrements in lung function did not persist to age 15 years, possible effects on the lung of early exposure to PM (especially from road traffic) may be transitory or reflect toxicity of the air pollution mix in the fetal and early life period.

General air quality improved over our study period(33), and the proportional contribution of diesel emissions became progressively less. Diesel emissions, believed to be particularly toxic to the developing lungs(5), are likely to have contributed largely to PM concentrations in our study area during the pregnancy periods because regulations on PM emissions from diesel vehicles were first introduced in the UK in July 1992 (i.e. Euro 1). Prior to Euro 1 regulations, PM_{10} emissions from diesel vehicles were about 0.17 gram per kilometre driven. This reduced by many orders of magnitude (i.e. <0.01 g/km) by 2009 with progressively tightening of regulations, for example, through the fitting of diesel particulate filters(39). Thus it is possible that negative effects of early-life exposure to higher, more toxic air pollution may have been offset by increased lung growth up to age 15 years in the absence of continued cumulative high exposure. This is supported by results of the Southern California Children's Health Study, in which long-term air quality improvements were associated with improvements in growth of both FEV_1 and FVC from aged 11 to 15 years(6).

Mechanisms of air pollution effects, particularly during pregnancy, on childhood lung function remain unclear. One likely central pathway is through oxidative stress (i.e. over-production of reactive oxygen species). It is believed that particles inhaled by the mother during pregnancy could cross the placental barrier(40) and directly disturb *in-utero* lung development via promotion of oxidative stress(9). Some recent studies have suggested that epigenetic changes induced by prenatal air pollution exposure may also play an important role(24, 41).

We found increased susceptibility to the effects of air pollution on lung function at mid-childhood among boys, consistent with several studies(6, 7, 14, 24) but not others that reported no differences between sexes(12, 22). Another finding of public health concern is that children from a lower socioeconomic background tended to be more susceptible, possibly as they were likely exposed to some other unfavourable exposures related to their socioeconomic disadvantage.

Our study has limitations. We relied on modelling of air pollution exposures at residential address and did not make allowance for travel patterns, or indoor pollution sources. The downward time trends in PM_{10} levels during follow-up may have potentially affected our results; however, as we previously documented that declines in PM_{10} levels during measurement of lung function at both 1999-2002 and 2006-2008 have been relatively small(33) and therefore substantial confounding due to time trends seems unlikely. As expected in any long-running birth cohort, there is loss to follow-up which may be differential. For example, children who were more socially deprived were more likely to drop out than socially advantaged children, although PM_{10}_road exposures in pregnancy and infancy as well as lung function measures at age 8 years were similar between groups(Table S8). This potential selection bias may in part explain the non-significant findings at age 15 years and affects generalizability of the observed findings.

We used separate models for each trimester-averaged exposure, but estimates may be biased if exposure in other trimesters act as unmeasured confounders, e.g. through seasonal trends in particulate exposure(42). This can be reduced by including all trimester-averaged exposures in a single model (not possible if there are high correlations between trimesters, e.g. PM_{10}_road and PM_{10}_other), or by using other statistical models. Wilson et al (42) used a distributed lag model considering exposures in each week of pregnancy but we were unable to implement this

model in this current analysis because we had too few data points and because the model requires data points to be of equal temporal length. Therefore we used a profile regression model designed to deal with correlated data points, which does not have a requirement about temporal spacing of data. This did not identify a specific susceptible trimester.

Only two time points of lung function measurements were available for our analyses. Compared to mid-childhood, it is difficult to study the effects of early-life air pollution exposure on lung function in adolescence. Throughout adolescence the rapid growth of lung function may follow a non-linear pattern and is dependent on sex as puberty plays a major role. Generally, lung volume growth in boys tends to occur rapidly towards the end of puberty whilst in girls this process starts earlier in puberty(43). Tobacco smoking is also an important factor impacting lung function growth; however our results did not change after further adjusting for smoking at age 15 years. We did not adjust dietary patterns during pregnancy or throughout childhood which might also have impacts on lung function.

In conclusion, exposure to road-traffic PM_{10} in pregnancy and early life was associated with small but significant reductions in lung function in mid-childhood. Although PM_{10} emissions from diesel vehicles have been declining over the years in the UK, other traffic-derived pollutants, such as NO_2, a good proxy of diesel emissions, are still found in high concentrations among many UK cities(44). A stringent control policy on road traffic-related air pollution is required to protect respiratory health of children with potential for long-term benefits on lung health across the life-course(1).

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The authors dedicate this work to the memory of Professor A John Henderson, a highly respected clinical expert and academic who led the programme of respiratory follow-up in the ALSPAC cohort and made enormous contributions to research into paediatric respiratory medicine and the epidemiology of respiratory disease in childhood.

REFERENCES

(1) Belgrave DCM, Granell R, Turner SW, Curtin JA, Buchan IE, Le Souef PN, Simpson A, Henderson AJ, Custovic A. Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. *Lancet Respir Med* 2018;6:526-534.

(2) Bui DS, Lodge CJ, Burgess JA, Lowe AJ, Perret J, Bui MQ, Bowatte G, Gurrin L, Johns DP, Thompson BR, Hamilton GS, Frith PA, James AL, Thomas PS, Jarvis D, Svanes C, Russell M, Morrison SC, Feather I, Allen KJ, Wood-Baker R, Hopper J, Giles GG, Abramson MJ, Walters EH, Matheson MC, Dharmage SC. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018;6:535-544.

(3) Royal College of Physicians. Every breath we take: the lifelong impact of air pollution. London: Report of a working party, RCP; 2016.

(4) Lange P, Celli B, Agusti A, Boje Jensen G, Divo M, Faner R, Guerra S, Marott JL, Martinez FD, Martinez-Camblor P, Meek P, Owen CA, Petersen H, Pinto-Plata V, Schnohr P, Sood A, Soriano JB, Tesfaigzi Y, Vestbo J. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2015;373:111-122.

(5) Gauderman WJ, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D, Lurmann F, Avol E, Kunzli N, Jerrett M, Peters J. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007;369:571-577.

(6) Gauderman WJ, Urman R, Avol E, Berhane K, McConnell R, Rappaport E, Chang R, Lurmann F, Gilliland F. Association of improved air quality with lung development in children. *N Engl J Med* 2015;372:905-913.

(7) Gehring U, Gruzieva O, Agius RM, Beelen R, Custovic A, Cyrys J, Eeftens M, Flexeder C, Fuertes E, Heinrich J, Hoffmann B, de Jongste JC, Kerkhof M, Klumper C, Korek M, Molter A, Schultz ES, Simpson A, Sugiri D, Svartengren M, von Berg A, Wijga AH, Pershagen G, Brunekreef B. Air pollution exposure and lung function in children: the ESCAPE project. *Environ Health Perspect* 2013;121:1357-1364.

(8) Hwang B, Chen Y, Lin Y, Wu X, Leo Lee Y. Relationship between exposure to fine particulates and ozone and reduced lung function in children. *Environmental Research* 2015;137:382-390.

(9) Korten I, Ramsey K, Latzin P. Air pollution during pregnancy and lung development in the child. *Paediatr Respir Rev* 2017;21:38-46.

(10) Molter A, Agius RM, de Vocht F, Lindley S, Gerrard W, Lowe L, Belgrave D, Custovic A, Simpson A. Long-term exposure to PM10 and NO2 in association with lung volume and airway resistance in the MAAS birth cohort. *Environ Health Perspect* 2013;121:1232-1238.

(11) Oftedal B, Brunekreef B, Nystad W, Madsen C, Walker SE, Nafstad P. Residential outdoor air pollution and lung function in schoolchildren. *Epidemiology* 2008;19:129-137.

(12) Rice MB, Rifas-Shiman SL, Litonjua AA, Oken E, Gillman MW, Kloog I, Luttmann-Gibson H, Zanobetti A, Coull BA, Schwartz J, Koutrakis P, Mittleman MA, Gold DR. Lifetime Exposure to Ambient Pollution and Lung Function in Children. *Am J Respir Crit Care Med* 2016;193:881-888.

(13) Rojas-Martinez R, Perez-Padilla R, Olaiz-Fernandez G, Mendoza-Alvarado L, Moreno-Macias H, Fortoul T, McDonnell W, Loomis D, Romieu I. Lung function growth in children with long-term exposure to air pollutants in Mexico City. *Am J Respir Crit Care Med* 2007;176:377-384.

(14) Schultz ES, Gruzieva O, Bellander T, Bottai M, Hallberg J, Kull I, Svartengren M, Melen E, Pershagen G. Traffic-related air pollution and lung function in children at 8 years of age: a birth cohort study. *Am J Respir Crit Care Med* 2012;186:1286-1291.

(15) Schultz ES, Hallberg J, Bellander T, Bergstrom A, Bottai M, Chiesa F, Gustafsson PM, Gruzieva O, Thunqvist P, Pershagen G, Melen E. Early-Life Exposure to Traffic-related Air Pollution and Lung Function in Adolescence. *Am J Respir Crit Care Med* 2016;193:171-177.

(16) Urman R, McConnell R, Islam T, Avol EL, Lurmann FW, Vora H, Linn WS, Rappaport EB, Gilliland FD, Gauderman WJ. Associations of children's lung function with ambient air pollution: joint effects of regional and near-roadway pollutants. *Thorax* 2014;69:540-547.

(17) Fuertes E, Bracher J, Flexeder C, Markevych I, Klumper C, Hoffmann B, Kramer U, von Berg A, Bauer CP, Koletzko S, Berdel D, Heinrich J, Schulz H. Long-term air pollution exposure and lung function in 15 year-old adolescents living in an urban and rural area in Germany: The GINIplus and LISAplus cohorts. *Int J Hyg Environ Health* 2015;218:656-665.

(18) Barone-Adesi F, Dent JE, Dajnak D, Beevers S, Anderson HR, Kelly FJ, Cook DG, Whincup PH. Long-Term Exposure to Primary Traffic Pollutants and Lung Function in Children: Cross-Sectional Study and Meta-Analysis. *PLoS One* 2015;10:e0142565.

(19) Milanzi EB, Koppelman GH, Smit HA, Wijga AH, Oldenwening M, Vonk JM, Brunekreef B, Gehring U. Air pollution exposure and lung function until age 16 years: the PIAMA birth cohort study. *Eur Respir J* 2018;52:10.1183/13993003.00218-2018. Print 2018 Sep.

(20) Jedrychowski WA, Perera FP, Maugeri U, Mroz E, Klimaszewska-Rembiasz M, Flak E, Edwards S, Spengler JD. Effect of prenatal exposure to fine particulate matter on ventilatory lung function of preschool children of non-smoking mothers. *Paediatr Perinat Epidemiol* 2010;24:492-501.

(21) Mortimer K, Neugebauer R, Lurmann F, Alcorn S, Balmes J, Tager I. Air pollution and pulmonary function in asthmatic children: effects of prenatal and lifetime exposures. *Epidemiology* 2008;19:550-7; discussion 561-2.

(22) Morales E, Garcia-Esteban R, de la Cruz OA, Basterrechea M, Lertxundi A, de Dicastillo MD, Zabaleta C, Sunyer J. Intrauterine and early postnatal exposure to outdoor air pollution and lung function at preschool age. *Thorax* 2015;70:64-73.

(23) Bougas N, Ranciere F, Beydon N, Viola M, Perrot X, Gabet S, Lezmi G, Amat F, De Blic J, Just J, Momas I. Traffic-related Air Pollution, Lung Function, and Host Vulnerability. New Insights from the PARIS Birth Cohort. *Ann Am Thorac Soc* 2018;15:599-607.

(24) Lee AG, Le Grand B, Hsu HL, Chiu YM, Brennan KJ, Bose S, Rosa MJ, Brunst KJ, Kloog I, Wilson A, Schwartz J, Morgan W, Coull BA, Wright RO, Baccarelli AA, Wright RJ. Prenatal fine particulate exposure associated with reduced childhood lung function and nasal epithelia GSTP1 hypermethylation: Sex-specific effects. *Respir Res* 2018;19:76-018-0774-3.

(25) Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* 2013;42:111-127.

(26) Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, Ring S, Nelson SM, Lawlor DA. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol* 2013;42:97-110.

(27) Cai Y, Hansell A, Granell R, Blangiardo M, Fecht D, Gulliver J, Henderson A, Elliott P. Prenatal, Early-life and lifetime exposure to air pollution and childhood lung function and asthma: the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study [abstract]. *Environ Health Perspect* 2018:https://ehp.niehs.nih.gov/doi/10.1289/isesisee.2018.P03.1140.

(28) American Thoracic Society. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995;152:1107-1136.

(29) Chinn S, Rona RJ. Height and age adjustment for cross sectional studies of lung function in children aged 6-11 years. *Thorax* 1992;47:707-714.

(30) Huls A, Kramer U, Gappa M, Muller-Brandes C, Schikowski T, von Berg A, Hoffmann B, Schuster A, Wisbauer M, Flexeder C, Heinrich J, Schulz H, Berdel D. Age Dependency of GLI Reference Values Compared with Paediatric Lung Function Data in Two German Studies (GINIplus and LUNOKID). *PLoS One* 2016;11:e0159678.

(31) Peralta GP, Fuertes E, Granell R, Mahmoud O, Roda C, Serra I, Jarvis D, Henderson J, Garcia-Aymerich J. Childhood Body Composition Trajectories and Adolescent Lung Function: Findings from the ALSPAC Study. *Am J Respir Crit Care Med* 2019.

(32) Boyd A, Thomas R, Hansell AL, Gulliver J, Hicks LM, Griggs R, Vande Hey J, Taylor CM, Morris T, Golding J, Doerner R, Fecht D, Henderson J, Lawlor DA, Timpson NJ, Macleod J. Data Resource Profile: The ALSPAC birth cohort as a platform to study the relationship of environment and health and social factors. *Int J Epidemiol* 2019.

(33) Gulliver J, Elliott P, Henderson J, Hansell AL, Vienneau D, Cai Y, McCrea A, Garwood K, Boyd A, Neal L, Agnew P, Fecht D, Briggs D, de Hoogh K. Local- and regional-scale air pollution modelling (PM10) and exposure assessment for pregnancy trimesters, infancy, and childhood to age 15years: Avon Longitudinal Study of Parents And Children (ALSPAC). *Environ Int* 2018;113:10-19.

(34) Jones A, Thomson D, Hort M, Devenish B. The U.K. Met Office's Next-Generation Atmospheric Dispersion Model, NAME III. 2007:580-589.

(35) Li KH, Raghunathan TE, Rubin DB. Large-Sample Significance Levels from Multiply Imputed Data Using Moment-Based Statistics and an F Reference Distribution. *Journal of the American Statistical Association* 1991;86:1065-1073.

(36) Molitor J, Papathomas M, Jerrett M, Richardson S. Bayesian profile regression with an application to the National Survey of Children's Health. *Biostatistics* 2010;11:484-498.

(37) Liverani S, Hastie DI, Papathomas MAL, Richardson S. PReMiuM: An R Package for Profile Regression Mixture Models Using Dirichlet Processes. *Journal of Statistical Software* 2015;64.

(38) Kajekar R. Environmental factors and developmental outcomes in the lung. *Pharmacol Ther* 2007;114:129-145.

(39) Emissions of Air Quality Pollutants 1990-2012. https://uk-air.defra.gov.uk/assets/documents/reports/cat07/1511261124_AQPI_Summary_1990-2012_Issue_v1.1.pdf: Department for Environment, Food and Rural Affairs, United Kingdom; 2015.

(40) Bove H, Bongaerts E, Slenders E, Bijnens EM, Saenen ND, Gyselaers W, Van Eyken P, Plusquin M, Roeffaers MBJ, Ameloot M, Nawrot TS. Ambient black carbon particles reach the fetal side of human placenta. *Nature Communications* 2019;10:3866.

(41) Plusquin M, Chadeau-Hyam M, Ghantous A, Alfano R, Bustamante M, Chatzi L, Cuenin C, Gulliver J, Herceg Z, Kogevinas M, Nawrot TS, Pizzi C, Porta D, Relton CL, Richiardi L, Robinson O, Sunyer J, Vermeulen R, Vriens A, Vrijheid M, Henderson J, Vineis P. DNA Methylome Marks of Exposure to Particulate Matter at Three Time Points in Early Life. *Environ Sci Technol* 2018;52:5427-5437.

(42) Wilson A, Chiu YM, Hsu HL, Wright RO, Wright RJ, Coull BA. Potential for Bias When Estimating Critical Windows for Air Pollution in Children's Health. *Am J Epidemiol* 2017;186:1281-1289.

(43) Neve V, Girard F, Flahault A, Boule M. Lung and thorax development during adolescence: relationship with pubertal status. *Eur Respir J* 2002;20:1292-1298.

(44) Mudway IS, Dundas I, Wood HE, Marlin N, Jamaludin JB, Bremner SA, Cross L, Grieve A, Nanzer A, Barratt BM, Beevers S, Dajnak D, Fuller GW, Font A, Colligan G, Sheikh A, Walton R, Grigg J, Kelly FJ, Lee TH, Griffiths CJ. Impact of London's low emission zone on air quality and children's respiratory health: a sequential annual cross-sectional study. *Lancet Public Health* 2019;4:e28-e40.

List of Figures

Figure 1a-1c Mean changes in percent predicted of lung function at both age 8 and 15 years in relation to per 1μg/m^3 higher PM_{10}_road at different time periods, fully adjusted model*

*adjusted for sex, gestational age, maternal education, home ownership, maternal smoking during pregnancy, passive smoking in childhood, damp and mould presence at home, and season of clinic visit; WP-whole pregnancy

Figure 2a-2c Mean changes in percent predicted of lung function at both aged 8 and 15 years in relation to per 10μg/m^3 higher PM_{10}_ total at different time periods, fully adjusted model*

*adjusted for sex, gestational age, maternal education, home ownership, maternal smoking during pregnancy, passive smoking in childhood, damp and mould presence at home, and season of clinic visit; WP-whole pregnancy

Figure 3 Mean changes in percent predicted of FVC at aged 8 years in relation to per 1μg/m^3 higher PM_{10}_ road at different time periods by maternal education, smoking and sex, fully adjusted model*

*adjusted for sex, gestational age, maternal education, home ownership, maternal smoking during pregnancy, passive smoking in childhood, damp and mould presence at home, and season of clinic visit; WP-whole pregnancy

Table 1 Summary statistics of the study populations

	Entire cohort (N=13963)		Age 8 years (N=5276ł)		Age 15 years (N=3446ł)	
Characteristic	N	%	N	% or Mean(SD)	N	% or Mean(SD)
male sex	7213/13963	52%	2664/5276	50%	1682/3446	49%
preterm birth (<37 weeks)	844/13963	6%	305/5276	6%	173/3446	5%
lower maternal education	8017/12403	65%	2843/5082	56%	1802/3348	54%
maternal smoking in pregnancy	3293/13144	25%	944/5174	18%	531/3385	16%
rented a home in the first 8 months	2290/10939	21%	630/4833	13%	378/3151	12%
presence of damp/mould at home in the first 8 months	5352/11226	48%	2357/4911	48%	1616/3214	50%
ever exposed to passive smoking in childhood	6654/10188	65%	2587/4662	55%	1574/3044	52%
never had breastfeeding	2755/11313	24%	905/4959	18%	496/3247	15%
current asthma			464/4460	10%	230/2299	10%
current body mass index (BMI), kg/m^2			4979	17.1 (2.4)	3441	21.5 (3.5)
FEV_1, litre			5276	1.69(0.26)	3446	3.45(0.78)
FEV_1, %predicted			5276	99.22%(11.67)	3446	93.66%(15.65)
FVC, litre			5276	1.92(0.31)	3446	3.76(0.88)
FVC, %predicted			5276	99.04%(11.92)	3446	89.05%(14.88)
FEV_1/FVC			5276	0.88(0.06)	3446	0.92(0.07)

FEV^1/FVC, %predicted	5276	99.71%(7.08)	3446	104.83%(7.72)

łparticipants had data on at least FEV_1 or FVC %predicted valuesat the current age; SD=standard deviation

Table 2 Distributions of air pollutants (μg/m^3) at different time periods

PM_{10} component	Exposure period	N	Mean	SD	Median	IQR	Range
PM_{10}_road	T1, *daily average*	12,445	0.96	0.71	0.80	0.72	0.07-7.80
	T2, *daily average*	12,726	0.96	0.71	0.80	0.71	0.10-8.37
	T3, *daily average*	12,670	0.94	0.69	0.78	0.70	0.05-7.26
	Whole pregnancy, *daily average*	12,315	0.96	0.69	0.81	0.72	0.13-7.72
	0-6months, *daily average*	12,538	0.94	0.68	0.79	0.73	0.14-8.33
	7-12months, *daily average*	12,440	0.89	0.65	0.75	0.68	0.13-7.17
	0-7 years, *annual average*	10,974	0.97	0.46	0.93	0.54	0.23-4.78
	8-15 years, *annual average*	11,181	0.65	0.28	0.67	0.33	0.13-3.75
	0-15 years, *annual average*	10,309	0.80	0.35	0.80	0.41	0.18-3.63
PM_{10}_other	T1, *daily average*	12,445	5.24	1.97	5.10	2.42	0.78-18.36
	T2, *daily average*	12,726	5.25	1.96	5.08	2.41	0.79-19.07
	T3, *daily average*	12,670	5.17	1.94	5.06	2.42	0.86-19.32

	Whole pregnancy, *daily average*	12,315	5.24	1.85	5.20	2.30	1.12-17.14
	0-6months, *daily average*	12,538	5.19	1.88	5.14	2.37	1.05-19.47
	7-12months, *daily average*	12,440	4.87	1.76	4.83	2.23	1.08-18.07
	0-7 years, *annual average*	10,974	4.62	1.35	4.77	1.83	1.30-13.07
	8-15 years, *annual average*	11,181	2.70	0.80	2.93	1.04	0.66-6.41
	0-15 years, *annual average*	10,309	3.60	1.01	3.78	1.35	0.97-9.39
PM_{10}_total	T1, *daily average*	12,445	33.45	5.31	32.88	7.90	20.38-54.21
	T2, *daily average*	12,726	32.97	5.35	31.97	7.86	20.65-56.78
	T3, *daily average*	12,670	31.49	5.26	30.40	6.87	17.08-67.83
	Whole pregnancy, *daily average*	12,315	32.58	2.98	32.60	3.79	22.82-48.52
	0-6months, *daily average*	12,538	31.82	3.74	31.57	5.08	22.37-51.76
	7-12months, *daily average*	12,440	30.96	3.12	30.83	4.29	22.51-49.72
	0-7 years, *annual average*	10,974	32.99	1.83	33.08	2.50	28.20-42.91
	8-15 years, *annual average*	11,181	22.98	1.05	23.19	1.44	20.19-27.25
	0-15 years, *annual average*	10,309	27.66	1.36	27.82	1.85	24.03-34.54

T1 – first trimester; T2- second trimester; T3 – third trimester; IQR – Interquartile range; SD: standard deviation