

**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

## **DESCRIPTOR NUMBER:**

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<sub>10</sub> from all sources but for PM<sub>10</sub> 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](http://www.atsjournals.org) .

## **WORD COUNT**

3,636 words



## 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  $\leq 10\mu\text{m}$  ( $\text{PM}_{10}$ ) 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 ( $\text{FEV}_1$ ) and forced vital capacity (FVC) at ages 8 ( $N=5,276$ ) and 15 ( $N=3,446$ ) years, using linear 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  $\text{PM}_{10}$  from road-traffic: at age 8 years,  $1\mu\text{g}/\text{m}^3$  higher exposure during the first trimester was associated with lower %predicted of  $\text{FEV}_1$  (-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  $\text{PM}_{10}$  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  $\text{PM}_{10}$  during pregnancy may result in small but significant reductions in lung function at age 8 years.

25 Word count: 247 words

26 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<sub>1</sub>) 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<sub>1</sub>, Forced Vital Capacity (FVC), and FEV<sub>1</sub>/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  $\leq 10\mu\text{m}$  (PM<sub>10</sub>) from local major road traffic (PM<sub>10\_road</sub>, 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<sub>10</sub> emissions on a 1x1km grid from other local combined sources such as industrial, domestic or minor roads (PM<sub>10\_other</sub>, hereafter) were obtained by subtracting summed emission rates from main roads from total PM<sub>10</sub> emission using the National Atmospheric Emissions Inventory (<http://naei.beis.gov.uk/data/data-selector>, accessed February 2020); and total PM<sub>10</sub> (PM<sub>10\_total</sub>, hereafter) was a combination of PM<sub>10\_road</sub>, PM<sub>10\_other</sub>, 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<sub>10</sub> 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<sub>10</sub> concentrations (PM<sub>10\_road</sub>; PM<sub>10\_other</sub>) and total sources (PM<sub>10\_road</sub>, PM<sub>10\_other</sub>, anthropogenic, and non-anthropogenic background concentrations) were estimated every year after birth up to age 15 years.

## Statistical analyses

Average daily PM<sub>10</sub> exposures for each trimester, whole pregnancy, 0-6 months, 7-12 months and annual PM<sub>10</sub> 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<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC) at both ages 8 and 15 years. Effect estimates were presented

as per  $10\mu\text{g}/\text{m}^3$  increment in  $\text{PM}_{10}$ \_total exposure and per  $1\mu\text{g}/\text{m}^3$  increment in  $\text{PM}_{10}$ \_road and  $\text{PM}_{10}$ \_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  $<10^{\text{th}}$  percentile for gestational age vs.  $10^{\text{th}}$ + percentile).

Potential effect modifications by child’s sex, maternal education and maternal smoking were examined by adding into the models an interaction term between  $\text{PM}_{10}$  exposure and each of these variables.

Missing data of  $\text{PM}_{10}$  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  $\text{PM}_{10}$  exposures, covariates and outcomes at both ages 8 and 15 years were all available.

Spearman correlations between  $\text{PM}_{10}$  for different time periods were calculated. To investigate the independent effects of  $\text{PM}_{10}$ \_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  $\text{PM}_{10}$ \_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<sub>10</sub>\_total exposures were 33.45 µg/m<sup>3</sup> in the first trimester and declined in each subsequent period to 30.96 µg/m<sup>3</sup> by 7-12 months of age (Table 2). The annual average PM<sub>10</sub>\_total exposures for 0-7 years and 8-15 years was 32.99 µg/m<sup>3</sup> and 22.98 µg/m<sup>3</sup> 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<sub>10</sub>\_road for different time periods were highly correlated(TableS2.1), as also seen for PM<sub>10</sub>\_other(TableS2.2). In contrast, correlations between PM<sub>10</sub>\_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<sub>10</sub> exposure ranged from 0.48 to 0.96(TableS3).

For PM<sub>10</sub>\_road, each 1µg/m<sup>3</sup> higher exposure during the first trimester was associated with lower %predicted of FEV<sub>1</sub> (-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<sub>1</sub> 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<sub>1</sub>/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<sub>10</sub> 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<sub>10\_road</sub> 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<sub>10\_road</sub> 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<sub>1</sub> (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<sub>10\_other</sub>, directions of associations at both ages were similar to those of PM<sub>10\_road</sub>, although the effect sizes were smaller and most significant associations did not persist after multiple test correction(FigureS4 a-c).

For PM<sub>10</sub>\_total, associations with both %predicted of FEV<sub>1</sub> 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<sub>1</sub>(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<sub>1</sub>/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<sub>1</sub> or FVC, and between the third trimester exposure and %predicted of FEV<sub>1</sub>/FVC ratio, although none of these persisted after multiple test corrections.

At age 8 years, for the associations between PM<sub>10</sub>\_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<sub>10</sub>\_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<sub>10</sub> exposure of each source during the first trimester and FEV<sub>1</sub> growth(Table S7).

## DISCUSSION

In this large cohort followed from antenatal period to age 15+ years, PM<sub>10</sub> 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<sub>10</sub> 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<sub>10</sub> 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<sub>10</sub> (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<sub>10</sub> exposure equates to an average decrement of about 14mL FEV<sub>1</sub> 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<sub>2</sub>) or PM with an aerodynamic diameter  $\leq 2.5\mu\text{m}$ (PM<sub>2.5</sub>)), small numbers and different characteristics of the study children (e.g. asthmatics, pre-schooler). PM<sub>2.5</sub> estimates were not modelled in our study as PM<sub>2.5</sub> monitoring data only became available from 2008 in Bristol and the surrounding areas(33). Nevertheless, our modelled estimates of PM<sub>10\_road</sub> should be qualitatively comparable to NO<sub>2</sub>, NO<sub>x</sub> or PM<sub>2.5</sub>, as all are likely to be primarily derived from road traffic sources.



The negative association of PM<sub>10</sub> 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<sub>2</sub> or PM<sub>2.5</sub>. 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<sub>2</sub> was significantly associated with a 28 ml and 33 ml reduction of FEV<sub>1</sub> and FVC respectively(22). Similarly, an earlier study in California of 232 asthmatic children age 6-11 years reported that FEV<sub>1</sub> and FVC was reduced by 1.2% and 7.1% for each IQR higher second trimester exposure to NO<sub>2</sub>, 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<sub>2.5</sub> in late pregnancy ( $\geq 35$  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<sub>1</sub> or FVC in relation to monitoring-based nitrogen oxides (NO<sub>x</sub>) exposures in each pregnancy trimester(23).

Unlike previous studies(21, 22, 24), we did not observe an effect from PM<sub>10\_road</sub> 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<sub>10\_road</sub>), it is difficult to be certain of a critical time window. We did not identify a specific sensitive trimester in relation to PM<sub>10\_road</sub> in the profile regression, but found lower mean FEV<sub>1</sub> and FVC in children with consistently high exposure to PM<sub>10\_road</sub> 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<sub>10</sub>, PM<sub>2.5</sub> or NO<sub>2</sub> at birth and age four years was significantly associated with reduced growth in FEV<sub>1</sub> 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<sub>1</sub> 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<sub>10</sub> 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<sub>10</sub> 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<sub>1</sub> 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<sub>10</sub> levels during follow-up may have potentially affected our results; however, as we previously documented that declines in PM<sub>10</sub> 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<sub>10\_road</sub> 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<sub>10\_road</sub> and PM<sub>10\_other</sub>), 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<sub>10</sub> in pregnancy and early life was associated with small but significant reductions in lung function in mid-childhood. Although PM<sub>10</sub> emissions from diesel vehicles have been declining over the years in the UK, other traffic-derived pollutants, such as NO<sub>2</sub>, 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.

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## 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  $1\mu\text{g}/\text{m}^3$  higher  $\text{PM}_{10\_road}$  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  $10\mu\text{g}/\text{m}^3$  higher  $\text{PM}_{10\_total}$  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  $1\mu\text{g}/\text{m}^3$  higher  $\text{PM}_{10\_road}$  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

Characteristic	Entire cohort (N=13963)		Age 8 years (N=5276†)		Age 15 years (N=3446†)	
	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 <sup>2</sup>			4979	17.1 (2.4)	3441	21.5 (3.5)
FEV <sub>1</sub> , litre			5276	1.69(0.26)	3446	3.45(0.78)
FEV <sub>1</sub> , %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 <sub>1</sub> /FVC			5276	0.88(0.06)	3446	0.92(0.07)

FEV <sub>1</sub> /FVC, %predicted	5276	99.71%(7.08)	3446	104.83%(7.72)
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†participants had data on at least FEV<sub>1</sub> or FVC %predicted values at the current age; SD=standard deviation

Table 2 Distributions of air pollutants ( $\mu\text{g}/\text{m}^3$ ) at different time periods

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

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





## Online Supplementary Files

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

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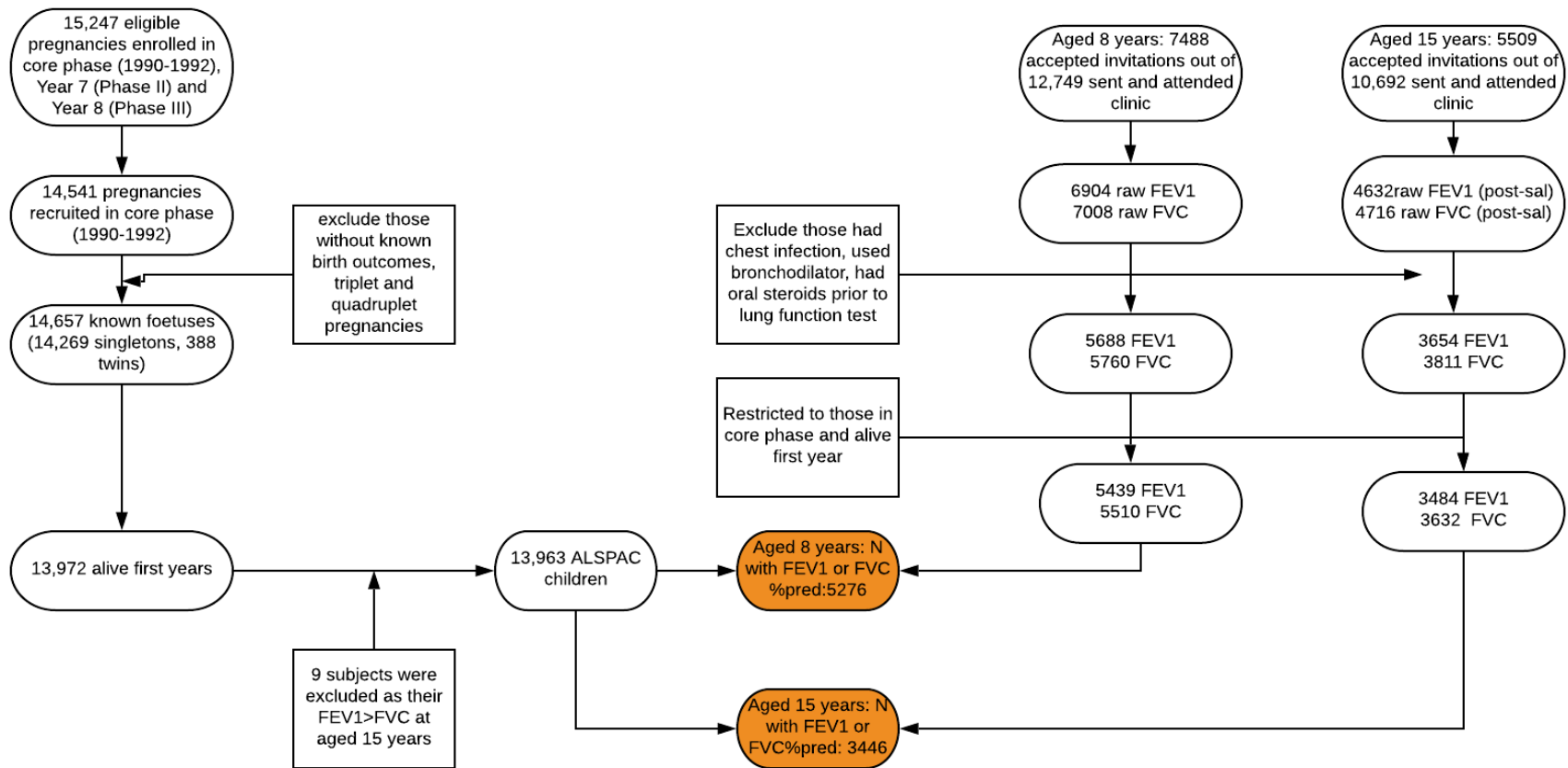
9: Health Data Research UK – London, London, UK

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Δ Equally supervised this study

†Deceased

Figure S1 –flowchart of study populations



## Supplementary text on Bayesian profile regression model

We applied the Bayesian profile regression model to a population of 13,963 children tested in order to measure their lung function. The population was partitioned in two groups taking into account the age of the measurements (8 and 15 years old age).

Eighteen covariates were considered in the model. Nine were confounders and treated as fixed effects in the model, and eight were continuous covariates mainly related to environmental factors.

We had six response variables (continuous), three related to the 8 years old group and three related to the 15 years old group.

In order to fit the Bayesian profile regression model, we needed to remove all the NAs from the outcome variables and the confounders. After filtering out the missing values we had a total of 4,214 observations for 8 years old and 2,772 for 15 years old.

We have assumed that the response variable model was Normal, as well as the covariates one. We used the default values for all hyperparameters for the 8 years old group. For the 15 years old one, we used all the default values except for  $p(\alpha)$  in this case following a *Gamma* (1,2) distribution.

The other specification for the hyperparameters were:

Dirichlet conjugate priors with  $a_j = -2$ , this setting allowed the parameter for random variation for the covariates and

$$p(\alpha) \equiv \text{Gamma}(2,1)$$

$$p(\theta_c) \equiv t_7(0,2.5)$$

$$p(\beta) \equiv t_7(0,2.5)$$

Where *Gamma*  $(\alpha, \beta) \equiv \frac{\beta^\alpha}{\Gamma(\alpha)} x^{\alpha-1} e^{-\beta x}$  and

$$t_v(\mu, \sigma) \equiv \frac{\Gamma(v+1/2)}{\Gamma(v/2)\sqrt{\pi v\sigma}} \left[ 1 + \frac{1}{v} \left( \frac{x-\mu}{\sigma} \right)^2 \right]^{-\frac{v+1}{2}}$$

We initialised all chains allocating subject randomly to 20 groups. We ran the chain for 10,000 after a burn-in sample of 20,000 iteration for the 8 years old group, and the chain for 20,000 and an initial burn-in of 30,000 iteration for the 15 years old one.

To assess that our MCMC chains have converged to the posterior probability distribution is a very complex problem, in order to verify if there was any evidence against it we used some graphical tools available for diagnostics from the R packages: PReMiuM and coda. In particular, we analysed the traces and the shape of the posterior distribution of the global parameters such as number of cluster (to check if the number we set a priori was big enough to allow for the convergence), alpha and beta and we obtained positive results.

Due to the problem of label switching it is not correct to simply assign each observation to the cluster which maximizes the average posterior probability. In order to deal with it the algorithm choses the partition based on a posterior similarity

matrix. At each iteration, a pairwise cluster membership is recorded and construct a score matrix. The average of these matrices over the whole MCMC runs leads to a similarity matrix  $S$  used to identify the optimal partition.

In particular, the optimal partition selection is implemented through the PAM (Partitioning Around Medoids Algorithm) on the dissimilarity matrix  $1-S$ . A final cluster is chosen by maximizing the average silhouette width across these best PAM partitions. For the 8 years group the best partition was composed by three clusters: cluster one ( $\sim 40$  children), cluster two ( $\sim 560$  children) and cluster three ( $\sim 3,600$  children), the silhouette index associated to the clustering in the best partition is about 0.88 for all the three outcome variables. In the case of the 15 years old group, the number of clusters in the best partition was different for the three outcome variables. For fev1 the number of cluster was 2: cluster 1 ( $\sim 2000$ ) and cluster 2 ( $\sim 500$ ) with a silhouette index of about 0.76, for fvc the number of cluster was 3: cluster 1 ( $\sim 40$ ), cluster 2 ( $\sim 2000$ ), and cluster 3 ( $\sim 500$ ) with a silhouette index of about 0.76, and for ratio we obtained again 2 clusters: cluster 1 ( $\sim 500$ ), cluster 2 ( $\sim 2000$ ) with a silhouette index of about 0.77. Since the values of the silhouette index are close to 1 for both the groups across all the outcome variables, it appears that the distance between the clusters is well defined.

Given the optimal partition, we have then assessed if the algorithm was consistently clustering individuals according with the best partition, in order to ensure narrower credibility intervals.

The boxplots show the posterior distribution for the probabilities of the response and the covariates for the three clusters that form the representative clustering for the 8 years old group and the 15 years old one for all the outcome variables.

With the aim to validate the obtained results we have then defined four pseudo profiles: 1) with the maximum values for all the covariates, 2) with the minimum values for all the covariates, 3) we have considered the maximum value for the covariate `pm10_avg_t1` (related to the exposure to the pollutant  $PM_{10}$  in the first in-utero trimester) and NA for all the others, 4) we have considered the minimum value for the covariate `pm10_avg_t1` and NA for all the others.

The obtained beanplots show the same distribution for the pseudo profiles related to minimum and maximum values, confirming the uncertainty of the relation with the outcome variables. Moreover, since in the beanplots, we are representing the values of the outcome variables (instead of the mean) there may be an additional layer of variability to take into account. We have observed the same behaviour between the 8 years old group and the 15 years old one.

Noting that some of the covariates, especially in the 15 years old group, had a similar profile probabilities for all the clusters, we have adopted a variable selection approach, in order to identify the covariates not containing clustering support and exclude them. In the 8 years old group, all the covariates contribute to the clustering for all the outcome variables. In the 15 years old one, the contribution of the covariates for `fev1` and `ratio` is unclear, all of them contribute to `fvc`.

For further details about the statistical methodology and the `PRemiuM` package we refer to Liverani *et. al*, 2015.

## Reference

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.

Table S1 Average PM exposure ( $\mu\text{g}/\text{m}^3$ ) in each time period by child's sex, maternal education and maternal smoking.

	Sex			Education			Maternal smoking		
	boy	girl	p-value	lower	higher	p-value	yes	no	p-value
PM <sub>10_road</sub>									
T1	0.97	0.96	0.480	0.93	1.01	<0.001	1.00	0.95	0.003
T2	0.96	0.96	0.772	0.93	1.01	<0.001	0.99	0.95	0.006
T3	0.94	0.94	0.945	0.91	0.99	<0.001	0.97	0.93	0.004
WP	0.96	0.96	0.780	0.93	1.00	<0.001	0.99	0.95	0.004
0-6months	0.94	0.94	0.971	0.91	0.99	<0.001	0.97	0.93	0.001
7-12months	0.89	0.90	0.951	0.87	0.93	<0.001	0.92	0.88	0.004
0-7 years	0.97	0.97	0.955	0.95	0.99	<0.001	0.99	0.96	0.007
8-15 years	0.65	0.65	0.535	0.64	0.65	0.185	0.66	0.64	0.039
0-15 years	0.80	0.80	0.827	0.79	0.81	0.003	0.81	0.79	0.039
PM <sub>10_total</sub>	boy	girl	p-value	lower	higher	p-value	yes	no	p-value
T1	33.5	33.4	0.626	33.3	33.6	0.005	33.6	33.4	0.095
T2	33.0	33.0	0.729	32.8	33.2	<0.001	32.9	33.0	0.261
T3	31.5	31.5	0.823	31.3	31.7	0.002	31.5	31.5	0.816
WP	32.6	32.6	0.904	32.4	32.8	<0.001	32.6	32.6	0.652
0-6months	31.8	31.8	0.506	31.7	32.0	<0.001	32.0	31.7	<0.001
7-12months	31.0	31.0	0.936	30.8	31.2	<0.001	30.9	31.0	0.491
0-7 years	33.0	33.0	0.659	32.9	33.1	<0.001	33.1	32.9	0.007
8-15 years	23.0	23.0	0.717	23.0	23.0	0.630	23.0	22.9	0.004
0-15 years	27.7	27.7	0.926	27.6	27.9	0.016	27.7	27.6	0.016

Table S2.1. Spearman's correlation (rho.) between average modelled **PM<sub>10</sub>\_road** exposures for pregnancy trimesters, early infancy (months 1 to 6), and late infancy (months 7-12) and between modelled average PM<sub>10</sub>\_road exposures for later years. All correlations significant at the 0.01 level (2-tailed).

	<b>Trimester 1</b>	<b>Trimester 2</b>	<b>Trimester 3</b>	<b>0-6 months</b>	<b>7-12 months</b>	<b>0-7 years annual average</b>	<b>8-15 years annual average</b>	<b>0-15 years annual average</b>
Trimester 1	1							
Trimester 2	0.93	1						
Trimester 3	0.91	0.92	1					
0-6 months	0.92	0.91	0.93	1				
7-12 months	0.89	0.91	0.92	0.96	1			
0-7 years annual average	0.87	0.88	0.89	0.93	0.94	1		
8-15 years annual average	0.67	0.67	0.69	0.72	0.73	0.85	1	
0-15 years annual average	0.81	0.82	0.83	0.87	0.88	0.97	0.94	1

All correlations two-tailed; p<0.001.



Table S2.2. Spearman's correlation (rho.) between average modelled **PM<sub>10</sub>\_other** exposures for pregnancy trimesters, early infancy (months 0 to 6), late infancy (months 7-12) and between modelled average PM<sub>10</sub>\_other exposures for later years. All correlations significant at the 0.01 level (2-tailed).

	Trimester 1	Trimester 2	Trimester 3	0-6 months	7-12months	0-7 years annual average	8-15 years annual average	0-15 years annual average
Trimester 1	1							
Trimester 2	0.84	1						
Trimester 3	0.81	0.82	1					
0-6 months	0.87	0.83	0.86	1				
7-12 months	0.82	0.87	0.87	0.94	1			
0-7 years annual average	0.81	0.81	0.83	0.93	0.94	1		
8-15 years annual average	0.66	0.66	0.68	0.73	0.74	0.85	1	
0-15 years annual average	0.77	0.78	0.79	0.88	0.89	0.97	0.94	1

All correlations two-tailed;  $p < 0.001$ .

Table S2.3. Spearman's correlation (rho.) between average modelled **PM<sub>10</sub>\_total** exposures for pregnancy trimesters, early infancy (months 0 to 6), and late infancy (months 7-12) and between modelled average PM<sub>10</sub>\_total exposures for later years. All correlations significant at the 0.01 level (2-tailed).

	Trimester 1	Trimester 2	Trimester 3	0-6 months	7-12months	0-7 years annual average	8-15 years annual average	0-15 years annual average
Trimester 1	1							
Trimester 2	-0.04	1						
Trimester 3	-0.09	0.02	1					
0-6 months	0.44	-0.16	0.10	1				
7-12 months	0.08	0.72	0.22	0.02	1			
0-7 years annual average	0.39	0.37	0.38	0.68	0.60	1		
8-15 years annual average	0.31	0.32	0.37	0.50	0.50	0.88	1	
0-15 years annual average	0.37	0.36	0.39	0.63	0.58	0.98	0.95	1

All correlations two-tailed;  $p < 0.001$ .

Table S3. Spearman's correlation (rho.) between average modelled PM<sub>10\_road</sub>, PM<sub>10\_other</sub>, PM<sub>10\_total</sub> by pregnancy trimester (T1, T2, T3), early infancy (EI; months 0 to 6), and late infancy (LI; months 7-12). and between modelled average exposures for later years. All correlations significant at the 0.01 level (2-tailed).

	PM <sub>10_road</sub>		PM <sub>10_other</sub>		PM <sub>10_total</sub>
PM <sub>10_other</sub>	T1	0.75			
	T2	0.75			
	T3	0.75			
	0-6m	0.75			
	7-12m	0.75			
	0-7y <sup>#</sup>	0.80			
	8-15y <sup>#</sup>	0.82			
	0-15y <sup>#</sup>	0.82			
PM <sub>10_total</sub>	T1	0.48	T1	0.61	
	T2	0.48	T2	0.61	
	T3	0.52	T3	0.66	
	0-6m	0.59	0-6m	0.69	
	7-12m	0.62	7-12m	0.69	
	0-7y <sup>#</sup>	0.85	0-7y <sup>#</sup>	0.96	
	8-15y <sup>#</sup>	0.87	8-15y <sup>#</sup>	0.94	
	0-15y <sup>#</sup>	0.86	0-15y <sup>#</sup>	0.95	

All correlations two-tailed; p<0.00; <sup>#</sup> annual average

Table S4 Mean Changes in percent predicted of lung function at both aged 8 and 15 years in relation to exposure at different time periods:  
complete-case (N=1501) analysis based on fully adjusted model\*(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)

PM <sub>10</sub> _road, per 1 µg/m <sup>3</sup> higher						
time period	% predicted of FEV <sub>1</sub>		% predicted of FVC		% predicted of FEV <sub>1</sub> /FVC	
	Age 8 years	Age 15 years	Age 8 years	Age 15 years	Age 8 years	Age 15 years
Trimester 1	-0.044 (-0.934 to 0.846)	<b>2.016</b> <b>(0.815 to 3.216)</b>	0.089 (-0.821 to 0.999)	<b>1.678</b> <b>(0.528 to 2.828)</b>	-0.084 (-0.611 to 0.444)	0.264 (-0.311 to 0.840)
Trimester 2	-0.073 (-0.934 to 0.787)	<b>1.492</b> <b>(0.332 to 2.652)</b>	0.032 (-0.847 to 0.912)	<b>1.292</b> <b>(0.181 to 2.402)</b>	-0.052 (-0.562 to 0.458)	0.127 (-0.428 to 0.683)
Trimester 3	-0.155 (-1.064 to 0.754)	0.779 (-0.448 to 2.006)	-0.076 (-1.006 to 0.854)	0.719 (-0.455 to 1.894)	-0.044 (-0.583 to 0.495)	-0.036 (-0.623 to 0.550)
Whole pregnancy	-0.102 (-1.010 to 0.806)	<b>1.519</b> <b>(0.292 to 2.745)</b>	0.016 (-0.913 to 0.944)	<b>1.310</b> <b>(0.135 to 2.484)</b>	-0.068 (-0.606 to 0.470)	0.123 (-0.464 to 0.710)
0-6 Months	-0.196 (-1.113 to 0.720)	0.530 (-0.709 to 1.768)	-0.097 (-1.034 to 0.840)	0.422 (-0.763 to 1.608)	-0.027 (-0.570 to 0.516)	0.042 (-0.550 to 0.635)
7-12 Months	-0.177	0.618	0.014	0.577	-0.110	-0.038

	(-1.113 to 0.758)	(-0.646 to 1.881)	(-0.942 to 0.970)	(-0.632 to 1.787)	(-0.664 to 0.444)	(-0.642 to 0.566)
0-7 years	-0.074	0.724	0.001	0.688	0.017	-0.050
	(-1.342 to 1.195)	(-0.990 to 2.438)	(-1.296 to 1.298)	(-0.953 to 2.328)	(-0.734 to 0.769)	(-0.870 to 0.769)
8-15 years		1.578		1.633		-0.233
		(-1.334 to 4.490)		(-1.154 to 4.420)		(-1.625 to 1.159)
0-15 years		1.113		1.100		-0.117
		(-1.166 to 3.391)		(-1.080 to 3.281)		(-1.207 to 0.972)
PM <sub>10</sub> _total, per 10µg/m <sup>3</sup> higher						
	% predicted of FEV <sub>1</sub>		% predicted of FVC		% predicted of FEV <sub>1</sub> /FVC	
time period	Age 8 years	Age 15 years	Age 8 years	Age 15 years	Age 8 years	Age 15 years
Trimester 1	0.034	<b>1.650</b>	0.156	<b>1.612</b>	-0.105	-0.047
	(-1.212 to 1.280)	<b>(0.047 to 3.252)</b>	(-1.118 to 1.430)	<b>(0.078 to 3.145)</b>	(-0.843 to 0.633)	(-0.814 to 0.720)
Trimester 2	-0.088	1.232	0.389	1.193	-0.360	0.090
	(-1.392 to 1.216)	(-0.411 to 2.876)	(-0.944 to 1.723)	(-0.380 to 2.766)	(-1.133 to 0.412)	(-0.695 to 0.876)
Trimester 3	-0.109	0.272	-0.978	-0.267	0.744	0.562
	(-1.403 to 1.186)	(-1.400 to 1.944)	(-2.301 to 0.345)	(-1.868 to 1.333)	(-0.022 to 1.510)	(-0.236 to 1.361)
Whole pregnancy	-0.148	<b>3.158</b>	-0.397	2.571	0.257	0.572
	(-2.312 to 2.017)	<b>(0.345 to 5.971)</b>	(-2.611 to 1.816)	(-0.123 to 5.264)	(-1.026 to 1.540)	(-0.774 to 1.918)
0-6 Months	0.631	-0.035	0.893	-0.453	-0.259	0.478

	(-1.104 to 2.366)	(-2.344 to 2.274)	(-0.880 to 2.667)	(-2.663 to 1.756)	(-1.287 to 0.769)	(-0.625 to 1.581)
7-12 Months	0.035	2.111	0.283	2.445	-0.056	-0.496
	(-2.020 to 2.091)	(-0.616 to 4.839)	(-1.818 to 2.385)	(-0.164 to 5.055)	(-1.274 to 1.162)	(-1.800 to 0.808)
0-7 years	0.804	1.140	0.913	0.501	-0.021	0.648
	(-2.466 to 4.075)	(-3.291 to 5.570)	(-2.431 to 4.258)	(-3.740 to 4.742)	(-1.960 to 1.917)	(-1.469 to 2.765)
8-15 years		4.642		3.292		1.115
		(-3.025 to 12.308)		(-4.047 to 10.632)		(-2.550 to 4.779)
0-15 years		2.394		1.445		0.883
		(-3.488 to 8.276)		(-4.185 to 7.076)		(-1.928 to 3.694)

Figure S2 Posterior distribution of the parameters for FEV<sub>1</sub> at age 8 years for the representative clustering.

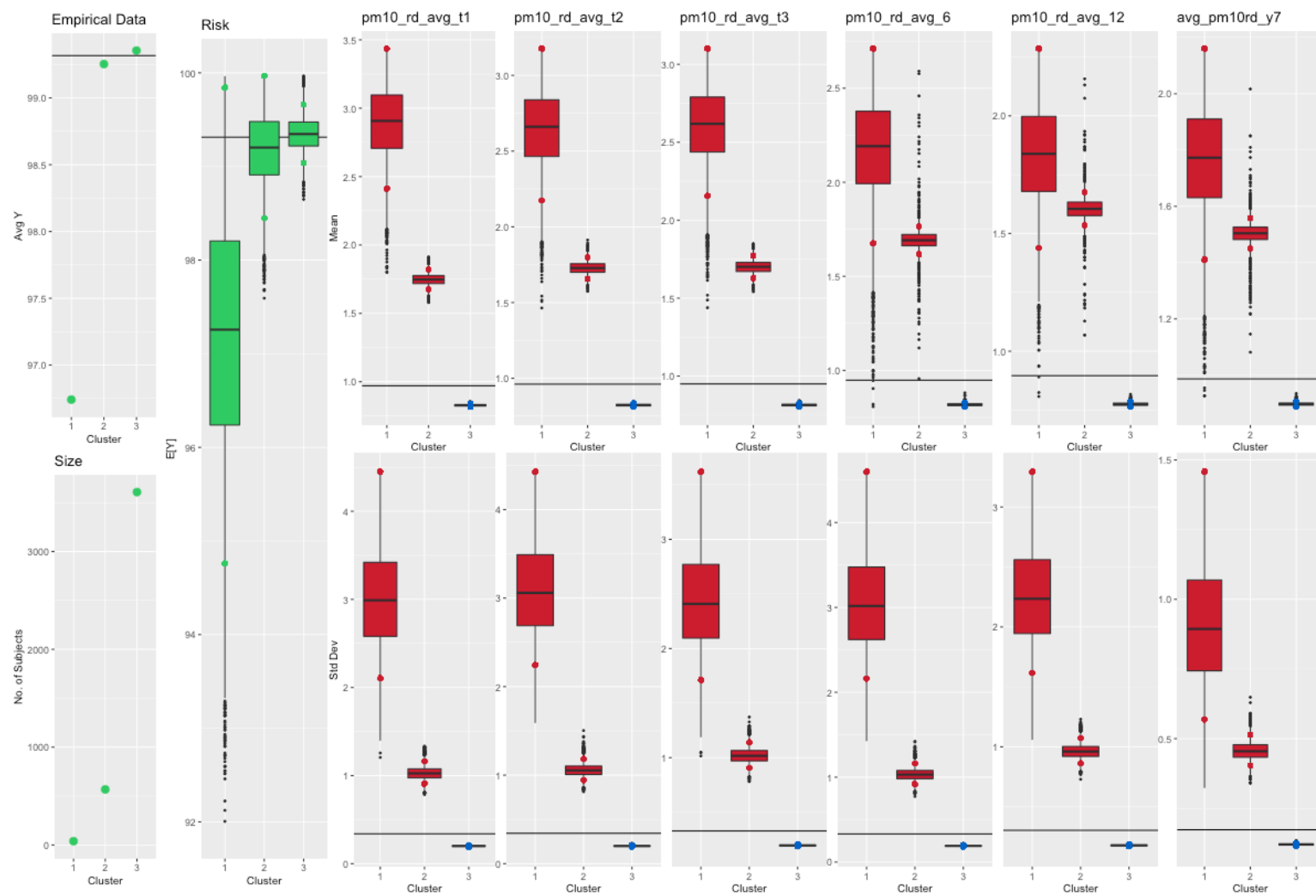


Figure S3 Posterior distribution of the parameters for FVC at age 8 years for the representative clustering.

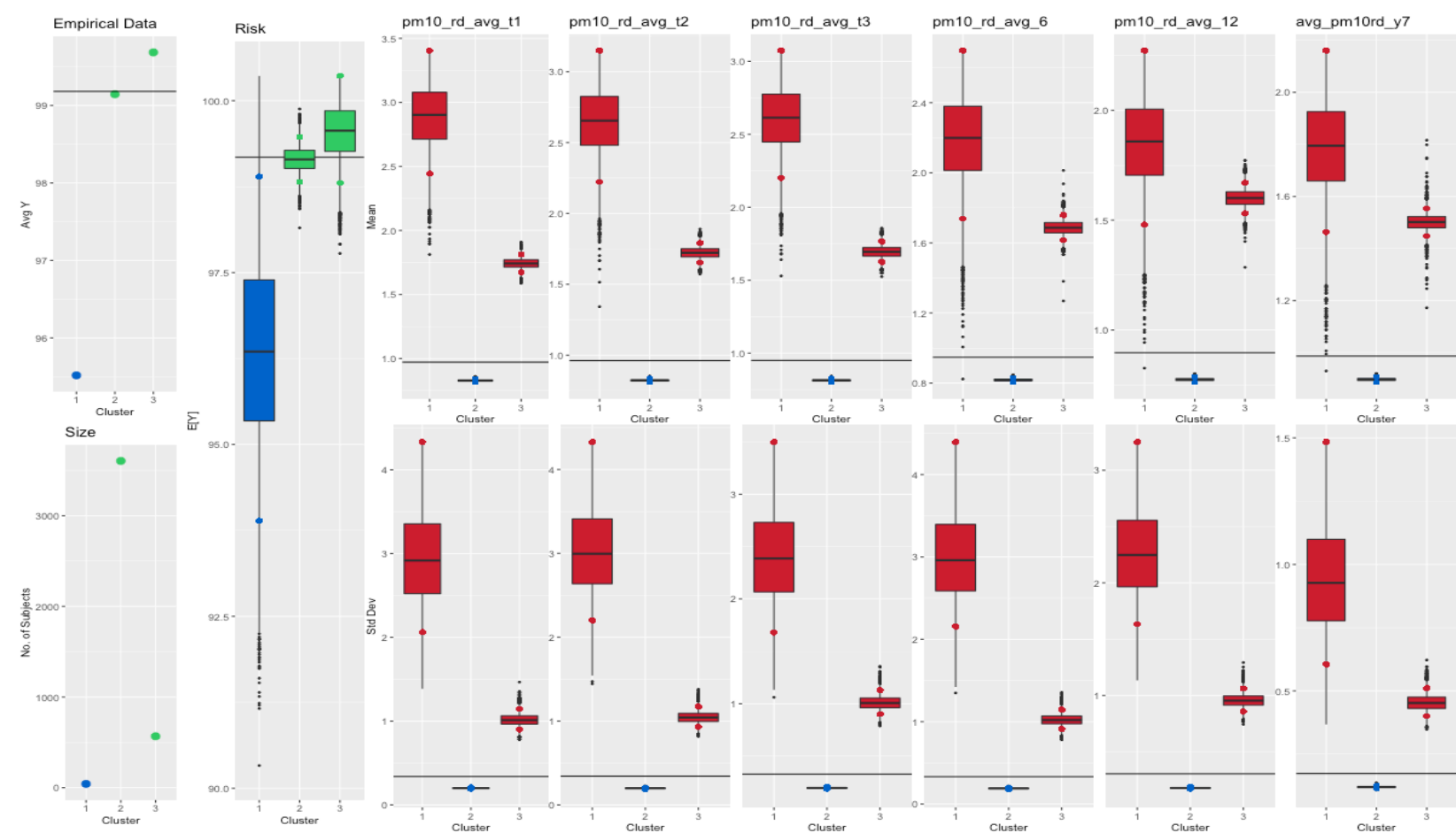
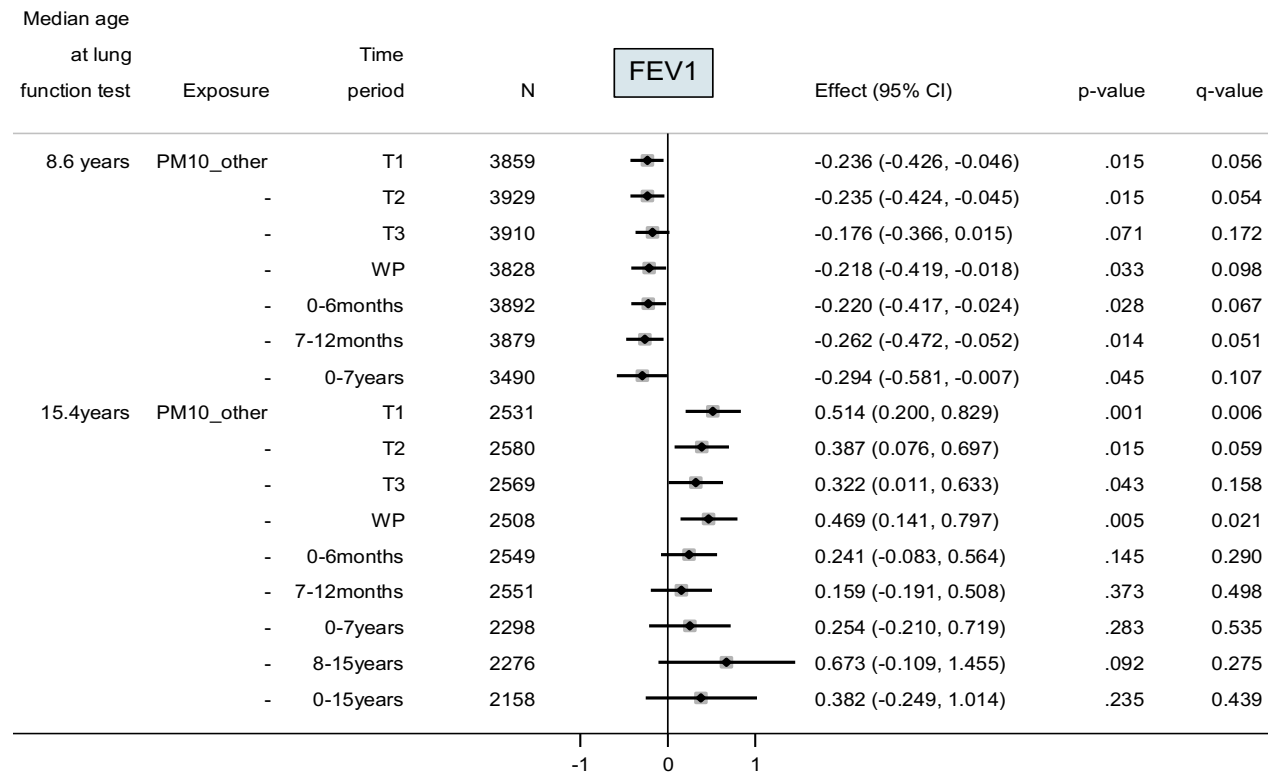
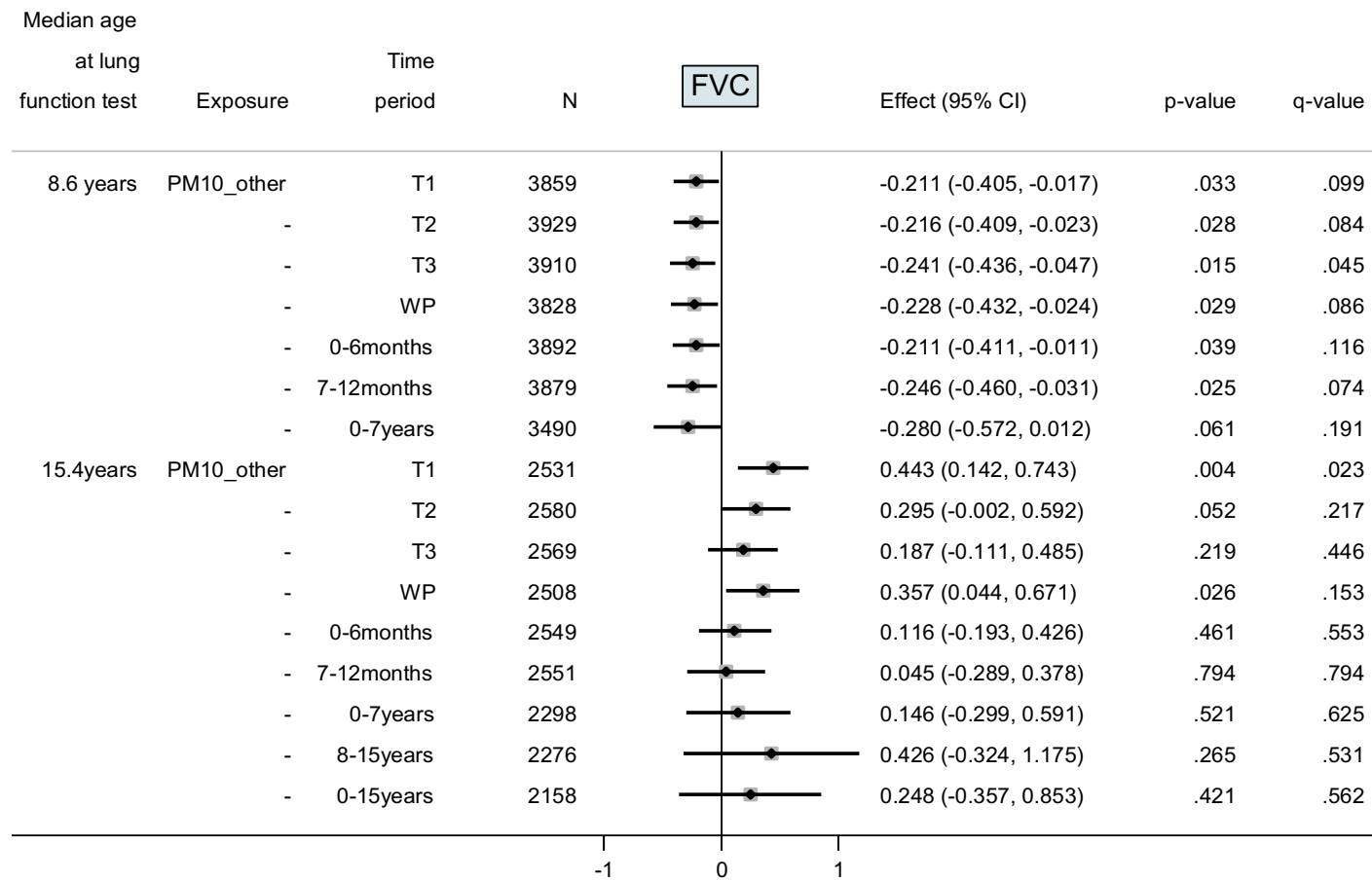




Figure S4 a-c: Mean Changes in percent predicted of lung function at both aged 8 and 15 years in relation to per 1  $\mu\text{g}/\text{m}^3$  higher **PM<sub>10</sub>\_other** at different time periods, main model\* (sex, gestational age, maternal education, home ownership, maternal smoking during pregnancy, passive smoking in childhood, damp and mould presence at home, and season of clinic visit)





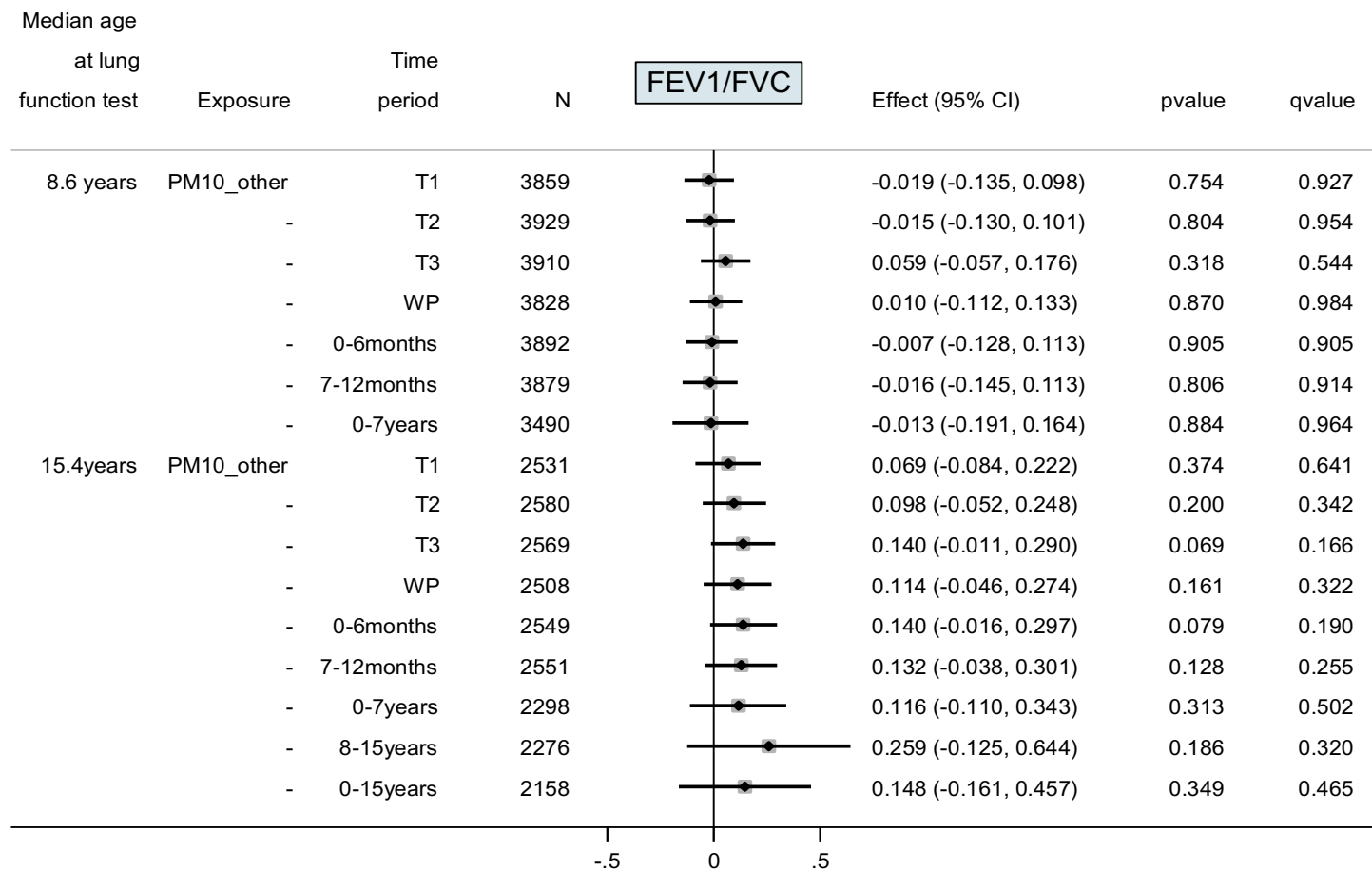


Table S5 Mean Changes in percent predicted of lung function at both aged 8 and 15 years in relation to per 10µg/m<sup>3</sup> higher **PM<sub>10</sub>\_total** at different time periods: co-adjusting PM<sub>10</sub>\_total exposures in preceding time periods based on main model\*(sex, gestational age, maternal education, home ownership, maternal smoking during pregnancy, passive smoking in childhood, damp and mould presence at home, and season of clinic visit)

% predicted of FEV <sub>1</sub> at aged 8 years						
	Main Model	Main Model +T1+T2	Main Model +T1+T2+T3	Main Model +T1+T2+T3+0-6 months	Main Model +T1+T2+T3+0-6 months+7-12 months	Main Model +T1+T2+T3+ 0-7 years
<b>Trimester 1</b>	-0.679 (-1.440 to 0.082)	-0.676 (-1.437 to 0.085) vif:1.20	-0.651 (-1.417 to 0.115) Vif:1.21	-0.662 (-1.542 to 0.219) Vif:1.58	-0.508 (-1.405 to 0.389) Vif: 1.61	-0.893 (-1.860 to 0.073) Vif:1.67
<b>Trimester 2</b>	<b>-0.930</b> <b>(-1.718 to -0.142)</b>	<b>-0.910</b> <b>(-1.702 to -0.119)</b> <b>vif: 1.29</b>	<b>-0.904</b> <b>(-1.700 to -0.108)</b> <b>Vif: 1.29</b>	<b>-0.953</b> <b>(-1.753 to -0.154)</b> <b>Vif: 1.29</b>	-0.463 (-1.649 to 0.723) Vif:2.81	-0.817 (-1.827 to 0.193) Vif:1.84
<b>Trimester 3</b>	-0.577 (-1.351 to 0.197)		-0.402 (-1.196to 0.392) Vif: 1.17	-0.459 (-1.266 to 0.348) Vif: 1.21	-0.238 (-1.098 to 0.623) Vif:1.35	-0.091 (-1.075 to 0.893) Vif:1.57
<b>0-6months</b>	-0.451 (-1.488 to 0.586)			0.172 (-1.046 to 1.389) Vif:1.48	0.176 (-1.061 to 1.412) Vif:1.51	-
<b>7-12 months</b>	<b>-2.045</b> <b>(-3.291 to -0.800)</b>				-1.162 (-3.174 to 0.850) Vif:2.64	-
<b>0-7 years</b>	<b>-2.498</b> <b>(-4.633 to -0.362)</b>					-0.304 (-3.494 to 2.886) Vif:2.19
% predicted of FVC at aged 8 years						

	Main Model	Main Model +T1+T2	Main Model +T1+T2+T3	Main Model +T1+T2+T3+0-6 months	Main Model +T1+T2+T3+0- 6months+7-12 months	Main Model +T1+T2+T3+ 0-7 years
<b>Trimester 1</b>	-0.468 (-1.244 to 0.308)	-0.473 (-1.249 to 0.303) Vif:1.20	-0.395 (-1.175 to 0.384) Vif:1.21	-0.496 (-1.392 to 0.400) Vif:1.58	-0.361 (-1.274 to 0.552) Vif:1.61	-0.628 (-1.611 to 0.354) Vif:1.67
<b>Trimester 2</b>	-0.610 (-1.414 to 0.194)	-0.572 (-1.379 to 0.235) Vif:1.29	-0.564 (-1.373 to 0.246) Vif:1.29	-0.595 (-1.409 to 0.219) Vif:1.29	-0.141 (-1.348 to 1.066) Vif:2.81	-0.315 (-1.342 to 0.712) Vif:1.84
<b>Trimester 3</b>	<b>-1.312</b> <b>(-2.100 to -0.525)</b>		<b>-1.202</b> <b>(-2.009 to -0.394)</b> <b>Vif:1.17</b>	<b>-1.229</b> <b>(-2.051 to -0.408)</b> <b>Vif:1.21</b>	<b>-1.038</b> <b>(-1.915 to -0.162)</b> <b>Vif:1.35</b>	-0.817 (-1.818 to 0.184) Vif:1.57
<b>0-6months</b>	-0.195 (-1.251 to 0.862)			0.406 (-0.834 to 1.645) Vif:1.48	0.379 (-0.880 to 1.638) Vif:1.51	-
<b>7-12 months</b>	<b>-1.805</b> <b>(-3.074 to -0.536)</b>				-1.058 (-3.107 to 0.990) Vif:2.64	-
<b>0-7 years</b>	-2.069 (-4.242to 0.105)					-0.147 (-0.392 to 3.098) Vif:2.19
% predicted of FEV <sub>1</sub> /FVC at aged 8 years						
	Main Model	Main Model +T1+T2	Main Model +T1+T2+T3	Main Model +T1+T2+T3+0-6 months	Main Model +T1+T2+T3+0- 6months+7-12 months	Main Model +T1+T2+T3+ 0-7 years
<b>Trimester 1</b>	-0.173 (-0.638 to 0.293)	-0.164 (-0.630 to 0.301) Vif:1.20	-0.211 (-0.679 to 0.256) Vif:1.21	-0.099 (-0.638 to 0.439) Vif:1.58	-0.086 (-0.634 to 0.462) Vif:1.61	-0.203 (-0.800 to 0.393) Vif:1.67
<b>Trimester 2</b>	-0.255 (-0.737 to 0.227)	-0.273 (-0.758 to 0.211) Vif:1.29	-0.275 (-0.761 to 0.211) Vif:1.29	-0.292 (-0.781 to 0.197) Vif:1.29	-0.311 (-1.036to 0.413) Vif:2.81	-0.413 (-1.036 to 0.210) Vif:1.84

<b>Trimester 3</b>	<b>0.641</b> <b>(0.168 to 1.113)</b>	<b>0.696</b> <b>(0.212 to 1.181)</b> <b>Vif:1.17</b>	<b>0.677</b> <b>(0.183 to 1.170)</b> <b>Vif:1.21</b>	<b>0.688</b> <b>(0.162 to 1.213)</b> <b>Vif:1.35</b>	<b>0.623</b> <b>(0.015 to 1.230)</b> <b>Vif:1.57</b>
<b>0-6months</b>	-0.268 (-0.903 to 0.368)		-0.278 (-1.023 to 0.467) Vif:1.48	-0.260 (-1.015 to 0.496) Vif:1.51	-
<b>7-12 months</b>	-0.140 (-0.903 to 0.622)			0.023 (-1.206 to 1.252) Vif:2.64	-
<b>0-7 years</b>	-0.388 (-1.709 to 0.933)				-0.198 (-2.166 to 1.771) Vif:2.19

% predicted of FEV <sub>1</sub> at aged 15 years						
	Main Model	Main Model +T1+T2	Main Model +T1+T2+T3	Main Model +T1+T2+T3+0-6 months	Main Model +T1+T2+T3+0- 6months+7-12 months	Main Model +T1+T2+T3+ 0-15 years
<b>Trimester 1</b>	<b>1.303</b> <b>(0.077 to 2.529)</b>	<b>1.374</b> <b>(0.145to 2.602)</b> <b>Vif:1.14</b>	<b>1.480</b> <b>(0.252 to 2.709)</b> <b>Vif:1.14</b>	<b>1.703</b> <b>(0.245 to 3.161)</b> <b>Vif:1.59</b>	<b>1.732</b> <b>(0.251 to 3.212)</b> <b>Vif:1.61</b>	<b>1.608</b> <b>(0.046 to 3.171)</b> <b>Vif:1.56</b>
<b>Trimester 2</b>	0.610 (-0.622 to 1.843)	0.660 (-0.576 to 1.896) Vif:1.20	0.661 (-0.575 to 1.898) Vif:1.20	0.580 (-0.667 to 1.826) Vif:1.20	-0.134 (-2.022 to 1.754) Vif:2.73	1.158 (-0.409 to 2.725) Vif:1.63
<b>Trimester 3</b>	0.008 (-1.191 to 1.206)		-0.006 (-1.244 to 1.231) Vif:1.14	-0.026 (-1.283 to 1.231) Vif:1.16	-0.404 (-1.771 to 0.963) Vif:1.36	0.260 (-1.291 to 1.810) Vif:1.49
<b>0-6months</b>	0.416 (-1.291 to 2.214)			-0.650 (-2.693 to 1.392) Vif:1.58	-0.887 (-2.958 to 1.183) Vif:1.61	-

<b>7-12 months</b>	1.330 (-0.723 to 3.282)				1.694 (-1.700 to 5.088 Vif:2.72	-
<b>0-15 years</b>	1.467 (-3.310 to 6.244)					-2.702 (-9.555 to 4.151) Vif:2.03
<b>% predicted of FVC at aged 15 years</b>						
	Main Model	Main Model +T1+T2	Main Model +T1+T2+T3	Main Model +T1+T2+T3+0-6 months	Main Model +T1+T2+T3+0- 6months+7-12 months	Main Model +T1+T2+T3+ 0-15 years
<b>Trimester 1</b>	<b>1.173</b> <b>(0.005 to 2.342)</b>	<b>1.204</b> <b>(0.033 to 2.376)</b> <b>Vif:1.14</b>	<b>1.303</b> <b>(0.131 to 2.476)</b> <b>Vif:1.14</b>	<b>1.821</b> <b>(0.429 to 3.213)</b> <b>Vif:1.59</b>	<b>1.751</b> <b>(0.339 to 3.163)</b> <b>Vif:1.61</b>	<b>1.633</b> <b>(0.139 to 3.127)</b> <b>Vif:1.56</b>
<b>Trimester 2</b>	0.491 (-0.688 to 1.669)	0.555 (-0.623 to 1.734) Vif:1.20	0.563 (-0.617 to 1.743) Vif:1.20	0.515 (-0.675 to 1.705) Vif:1.20	-0.740 (-2.541 to 1.061) Vif:2.73	1.008 (-0.490 to 2.506) Vif:1.63
<b>Trimester 3</b>	-0.582 (-1.728 to 0.564)		-0.564 (-1.744 to 0.617) Vif:1.14	-0.479 (-1.679 to 0.721) Vif:1.16	-1.041 (-2.346 to 0.263) Vif:1.36	-0.015 (-1.498 to 1.467) Vif:1.49
<b>0-6months</b>	-0.267 (-1.901 to 1.367)			-1.416 (-3.367 to 0.534) Vif:1.58	-1.755 (-3.731 to 0.220) Vif:1.61	-
<b>7-12 months</b>	1.236 (-0.723 to 3.194)				2.974 (-0.264 to 6.212) Vif:2.72	-
<b>0-15 years</b>	0.284 (-4.291 to 4.860)					-3.138 (-9.690 to 3.414) Vif:2.03
<b>%predicted of FEV<sub>1</sub>/FVC at aged 15 years</b>						
	Main Model	Main Model +T1+T2	Main Model +T1+T2+T3	Main Model +T1+T2+T3+0-6 months	Main Model +T1+T2+T3+0- 6months+7-12 months	Main Model +T1+T2+T3+ 0-15 years
<b>Trimester 1</b>	0.087 (-0.507 to 0.682)	0.136 (-0.460 to 0.733)	0.143 (-0.455 to 0.740)	-0.223 (-0.930 to 0.484)	-0.098 (-0.816 to 0.620)	-0.103 (-0.872 to 0.665)

		Vif:1.14	Vif:1.14	Vif:1.59	Vif:1.61	Vif:1.56
<b>Trimester 2</b>	0.147 (-0.448 to 0.742)	0.134 (-0.466 to 0.734) Vif:1.20	0.134 (-0.467 to 0.735) Vif:1.20	0.093 (-0.512 to 0.697) Vif:1.20	0.803 (-0.112 to 1.719) Vif:2.73	0.177 (-0.593 to 0.948) Vif:1.63
<b>Trimester 3</b>	<b>0.606</b> <b>(0.027 to 1.185)</b>		0.550 (-0.052 to 1.152) Vif:1.14	0.424 (-0.185 to 1.034) Vif:1.16	<b>0.677</b> <b>(0.013 to 1.340)</b> <b>Vif:1.36</b>	0.233 (-0.530 to 0.996) Vif:1.49
<b>0-6months</b>	0.796 (-0.031 to 1.622)			0.956 (-0.034 to 1.947) Vif:1.58	<b>1.089</b> <b>(0.084 to 2.093)</b> <b>Vif:1.61</b>	-
<b>7-12 months</b>	0.072 (-0.924 to 1.067)				<b>-1.675</b> <b>(-3.321 to -0.028)</b> <b>Vif:2.72</b>	-
<b>0-15 years</b>	1.325 (-1.014 to 3.664)					0.648 (-2.724 to 4.019) Vif:2.03



Figure S5 Mean Changes in percent predicted of FVC at aged 8 years in relation to per 10  $\mu\text{g}/\text{m}^3$  higher **PM<sub>10</sub>\_total** at different time periods by sex, maternal education and smoking, main model\*

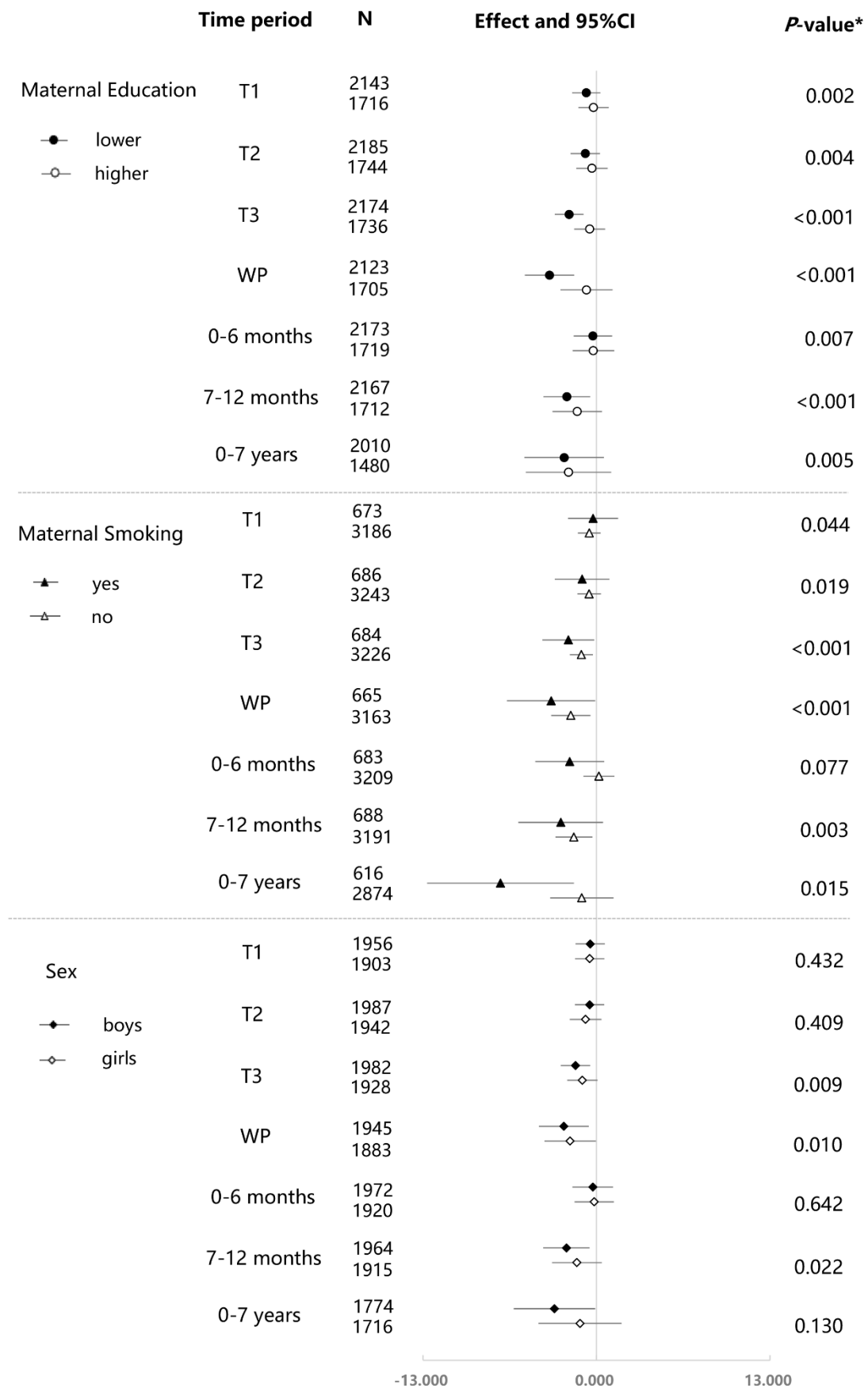


Table S6.1 Mean Changes in percent predicted of lung function at both aged 8 and 15 years in relation to per  $1\mu\text{g}/\text{m}^3$  higher **PM<sub>10\_road</sub>** at different time periods: sensitivity analyses based on fully adjusted model\*(sex, gestational age, maternal education, home ownership, maternal smoking during pregnancy, passive smoking in childhood, damp and mould presence at home, and season of clinic visit)

**Available as additional data in a large spreadsheet labelled as Table S6.1**

Table S6.2 Mean Changes in percent predicted of lung function at both aged 8 and 15 years in relation to per  $10\mu\text{g}/\text{m}^3$  higher **PM<sub>10\_total</sub>** at different time periods: sensitivity analyses based on main model(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)

**Available as additional data in a large spreadsheet labelled as Table S6.2**

Table S7 Associations between air pollution in different time periods and lung function growth in litres/year from age 8 to 15 years

	<b>PM<sub>10</sub>_total, per 10 µg/m<sup>3</sup></b>	<b>N</b>	<b>Effect(95%CI)</b>	<b>PM<sub>10</sub>_road, per 1 µg/m<sup>3</sup></b>	<b>N</b>	<b>Effect(95%CI)</b>	<b>PM<sub>10</sub>_other, per 1µg/m<sup>3</sup></b>	<b>N</b>	<b>Effect(95%CI)</b>
<b>FEV<sub>1</sub> growth</b>	Trimester 1	2129	<b>0.009 (0.002 to 0.016)</b>	Trimester 1	2129	<b>0.007 (0.002 to 0.012)</b>	Trimester 1	2129	<b>0.002 (0.001 to 0.004)</b>
	Trimester 2	2176	<b>0.007 (0.000 to 0.014)</b>	Trimester 2	2176	<b>0.005 (0.000 to 0.010)</b>	Trimester 2	2176	0.002 (-0.000 to 0.003)
	Trimester 3	2168	0.000 (-0.007 to 0.007)	Trimester 3	2168	0.003 (-0.002 to 0.008)	Trimester 3	2168	0.001 (-0.001 to 0.002)
	Whole pregnancy	2112	<b>0.015 (0.003 to 0.027)</b>	Whole pregnancy	2112	<b>0.006 (0.001 to 0.011)</b>	Whole pregnancy	2112	<b>0.002 (0.000 to 0.004)</b>
	0-6 months	2155	-0.003 (-0.012 to 0.006)	0-6 months	2155	0.003 (-0.002 to 0.008)	0-6 months	2155	0.000 (-0.001 to 0.002)
	7-12 months	2161	0.007 (-0.004 to 0.018)	7-12 months	2161	0.002 (-0.003 to 0.008)	7-12 months	2161	0.000 (-0.002 to 0.002)
	0-7 years	1945	-0.002 (-0.021 to 0.017)	0-7 years	1945	0.003 (-0.004 to 0.010)	0-7 years	1945	0.000 (-0.002 to 0.003)
	8-15 years	1924	0.017 (-0.016 to 0.050)	8-15 years	1924	0.009 (-0.003 to 0.022)	8-15 years	1924	0.003 (-0.001 to 0.007)
	0-15 years	1820	0.001 (-0.026 to 0.027)	0-15 years	1820	0.006 (-0.004 to 0.016)	0-15 years	1820	0.001 (-0.003 to 0.004)
<b>FVC growth</b>	Trimester 1	2195	<b>0.010 (0.002 to 0.017)</b>	Trimester 1	2195	0.005 (-0.0002 to 0.010)	Trimester 1	2195	<b>0.002 (0.000 to 0.004)</b>
	Trimester 2	2243	0.006 (-0.002 to 0.014)	Trimester 2	2243	0.004 (-0.001 to 0.009)	Trimester 2	2243	0.001 (-0.000 to 0.003)
	Trimester 3	2234	-0.004 (-0.012 to 0.003)	Trimester 3	2234	0.002 (-0.004 to 0.007)	Trimester 3	2234	0.000 (-0.002 to 0.002)
	Whole pregnancy	2177	0.010 (-0.002 to 0.023)	Whole pregnancy	2177	0.004 (-0.001 to 0.010)	Whole pregnancy	2177	0.001 (-0.000 to 0.003)
	0-6 months	2220	-0.007 (-0.018 to 0.003)	0-6 months	2220	0.002 (-0.004 to 0.007)	0-6 months	2220	0.000 (-0.002 to 0.002)
	7-12 months	2226	0.006	7-12 months	2226	0.002	7-12 months	2226	-0.000

		(-0.006 to 0.018)			(-0.004 to 0.007)			(-0.002 to 0.002)
0-7 years	2005	-0.008 (-0.029 to 0.012)	0-7 years	2005	0.002 (-0.006 to 0.010)	0-7 years	2005	-0.000 (-0.003 to 0.003)
8-15 years	1982	0.004 (-0.032 to 0.040)	8-15 years	1982	0.006 (-0.007 to 0.020)	8-15 years	1982	0.002 (-0.002 to 0.007)
0-15 years	1877	-0.008 (-0.037 to 0.020)	0-15 years	1877	0.005 (-0.006 to 0.016)	0-15 years	1877	0.000 (-0.003 to 0.004)

Table S8 Comparisons of characteristics, exposures and lung function between those remained and those lost to follow-up in this study

	Participated at age 8 years			Participated at age 15 years					
	yes (N=5276 )	no (n=8687)	p- value	yes (n=3446 )	no (n=10517 )	p- value	Participate d at both ages 8 and 15 years (n=2364)	Participated at age 8 but drop-out at age 15 years(n=2912 )	p- value
<b>preterm birth - yes</b>	5.8%	6.2%	0.308	5.0%	6.4%	0.004	4.7%	6.7%	0.002
<b>Maternal education level - lower</b>	55.9%	70.7%	<0.001	53.8%	68.6%	<0.001	51.3%	59.8%	<0.001
<b>Home ownership - rented</b>	13.0%	27.2%	<0.001	12.0%	24.5%	<0.001	11.0%	14.7%	<0.001
<b>Damp and mould presence at home - yes</b>	48.0%	47.4%	0.550	50.3%	46.6%	<0.001	49.0%	47.2%	0.209
<b>smoking in pregnancy - yes</b>	18.2%	29.5%	<0.001	15.7%	28.3%	<0.001	14.5%	21.3%	<0.001
<b>Exposure to passive smoke - yes</b>	55.5%	73.6%	<0.001	51.7%	71.1%	<0.001	49.9%	60.2%	<0.001
<b>PM<sub>10</sub>_road exposure in 1st trimester (mean(SD))</b>	0.96 (0.70)	0.97 (0.72)	0.626	0.96 (0.68)	0.97 (0.72)	0.610	0.95(0.67)	0.97(0.72)	0.457
<b>PM<sub>10</sub>_road exposure in 2nd trimester(mean(SD))</b>	0.96 (0.70)	0.96 (0.72)	0.615	0.96 (0.69)	0.96 (0.72)	0.931	0.96(0.69)	0.96(0.71)	0.999
<b>PM<sub>10</sub>_road exposure in 3rd trimester(mean(SD))</b>	0.94 (0.68)	0.94(0.70 )	0.994	0.94 (0.66)	0.94(0.70)	0.954	0.94(0.65)	0.94(0.71)	0.687
<b>FEV<sub>1</sub> in L at aged 8 years (mean(SD))</b>							1.70(0.26)	1.69(0.26)	0.608
<b>FVC in L at aged 8 years (mean(SD))</b>							1.92(0.31)	1.93(0.31)	0.736

