Ambient air pollution and low birthweight: a European cohort study (ESCAPE)

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Summary

Background Ambient air pollution has been associated with restricted fetal growth, which is linked with adverse respiratory health in childhood. We assessed the effect of maternal exposure to low concentrations of ambient air pollution on birthweight.

Methods We pooled data from 14 population-based mother–child cohort studies in 12 European countries. Overall, the study population included 74 178 women who had singleton deliveries between Feb 11, 1994, and June 2, 2011, and for whom information about infant birthweight, gestational age, and sex was available. The primary outcome of interest was low birthweight at term (weight <2500 g at birth after 37 weeks of gestation). Mean concentrations of particulate matter with an aerodynamic diameter of less than 2·5 μm ($PM_{2\cdot5}$), less than 10 μm (PM_{10}), and between 2·5 μm and 10 μm during pregnancy were estimated at maternal home addresses with temporally adjusted land-use regression models, as was $PM_{2\cdot5}$ absorbance and concentrations of nitrogen dioxide (NO_2) and nitrogen oxides. We also investigated traffic density on the nearest road and total traffic load. We calculated pooled effect estimates with random-effects models.

Findings A 5 μg/m^3 increase in concentration of $PM_{2\cdot5}$ during pregnancy was associated with an increased risk of low birthweight at term (adjusted odds ratio [OR] 1·18, 95% CI 1·06–1·33). An increased risk was also recorded for pregnancy concentrations lower than the present European Union annual $PM_{2\cdot5}$ limit of 25 μg/m^3 (OR for 5 μg/m^3 increase in participants exposed to concentrations of less than 20 μg/m^3 1·41, 95% CI 1·20–1·65). PM_{10} (OR for 10 μg/m^3 increase 1·16, 95% CI 1·00–1·35), NO_2 (OR for 10 μg/m^3 increase 1·09, 1·00–1·19), and traffic density on nearest street (OR for increase of 5000 vehicles per day 1·06, 1·01–1·11) were also associated with increased risk of low birthweight at term. The population attributable risk estimated for a reduction in $PM_{2\cdot5}$ concentration to 10 μg/m^3 during pregnancy corresponded to a decrease of 22% (95% CI 8–33%) in cases of low birthweight at term.

Interpretation Exposure to ambient air pollutants and traffic during pregnancy is associated with restricted fetal growth. A substantial proportion of cases of low birthweight at term could be prevented in Europe if urban air pollution was reduced.

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Introduction

Air pollution with ambient particulate matter is one of the most important controllable health threats.[1] Maternal exposure to air pollution during pregnancy could increase the risk of preterm birth (<37 weeks of gestation), low birthweight (<2500 g), congenital malformations, and other adverse health effects.[2–8]

Infants with low birthweight are at greater risk of mortality and morbidity than are infants with higher birthweight.[9–11] Low birthweight has been associated with wheezing and asthma in childhood,[12] and with decreased lung function in adults,[13] although findings are not consistent. Infants with low birthweight could have accelerated weight gain in the first 3 months of infancy, which has been associated with asthma symptoms in children aged up to 4 years.[14] In addition to active and passive smoking,[15] atmospheric pollution exposure is a highly prevalent and controllable potential risk factor for low birthweight.[2–8]

Meta-analyses[3–5] have shown heterogeneity of effects of air pollution across studies, but have suggested that particulate matter with an aerodynamic diameter of less than 2·5 μm ($PM_{2\cdot5}$) is most consistently associated with low birthweight. Exposure assessment in many previous studies of the effects of air pollution on fetal growth relied on routine air pollution monitoring stations, which do not capture within-city exposure contrasts adequately, possibly resulting in misclassification of exposure and

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possibly reduced risk estimates.[2–8,16] In studies in the past 7 years, methods such as land-use regression (LUR) have been applied to improve spatial resolution.[2–8,16–18] The largest body of evidence comes from a series of studies in the Los Angeles basin (CA, USA), where air pollution sources and mixtures could be different from those in smaller urban areas.[3–8] Apart from a few studies (usually based on birth registers[17,18]), many had small sample sizes or poor control of confounders.[2–8,16] The individual excess risk of low birthweight reported in these studies was low, but the large proportion of exposed women in the general population warrants an estimation of the attributable risk at the population level.

In this study, we investigated the associations of low levels of exposure to air pollutants with low birthweight at term, birthweight, and head circumference in a population from urban areas. We postulated that increased maternal exposure to ambient air pollution during pregnancy would be associated with intrauterine growth restriction. Additionally, we estimated the proportion of cases of low birthweight at term that were attributable to air pollution.

Methods

Study population

This study was part of the European Study of Cohorts for Air Pollution Effects (ESCAPE), in which the association between exposure to outdoor air pollution and health is being investigated with prospective cohort studies.[19] We pooled data from 14 European mother–child cohort studies in which birthweight was not part of inclusion criteria: MoBa (Norway); BAMSE (four centres; Sweden); DNBC (Denmark); KANC (Lithuania); BiB (England); ABCD, GENERATION R, and PIAMA (three centres; Netherlands); DUISBURG (Germany); EDEN (two centres; France), APREG (Hungary); GASPII (Italy); INMA (five centres; Spain); and RHEA (Greece; figure 1). Eligibility criteria were applied in each cohort (appendix p 4). Overall, the study population included 74 178 women who lived in the ESCAPE study areas;[19,20] had singleton deliveries between Feb 11, 1994, and June 2, 2011; and for whom information about home addresses during pregnancy, infant birthweight, gestational age, and sex was available.

Approval was obtained from the ethics committees in every site. All participating women provided informed consent—written or oral, or both, depending on the cohort—for themselves and their children.

Procedures

To ensure comparability of the information about maternal and child characteristics from the cohorts, variable definitions were standardised, and quality control was done centrally before data were pooled. We excluded women for whom more than 25% of values for LUR estimates or daily monitoring of air pollution were missing for the whole pregnancy exposure period and for each trimester.

The primary outcome of interest was low birthweight at term (ie, weight <2500 g at birth after 37 weeks of gestation). Other outcomes of interest were term birthweight and head circumference at birth. Information about gestational age, birthweight, head circumference, sex, and mode of delivery was obtained from birth records and questionnaires (appendix p 4).

Because of financial reasons, sampling of particulate matter was not done everywhere. Therefore, data for particulate matter are missing for the BiB and EDEN cohorts, and for four of the five INMA centres. That some data would be missing was known at the start of the project, and was considered during planning. Furthermore, because of scarce data for nitrogen dioxide (NO_2) and nitrogen oxides (NO_X) from the centralised routine air monitoring networks in Heraklion, Greece, it was not possible to back extrapolate NO_2 and NO_X for the RHEA cohort.

Annual mean concentrations of $PM_{2\cdot5}$ and particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}), of between 2·5 μm and 10 μm ($PM_{2\cdot5\text{–}10}$; coarse particulate matter), $PM_{2\cdot5}$ absorbance (a measure of black carbon), NO_2, and NO_X were estimated at the maternal home addresses with LUR models.[19,20] We examined $PM_{2\cdot5}$ absorbance to establish its role independently from that of $PM_{2\cdot5}$. $PM_{2\cdot5}$ absorbance provides a measure of particulate matter attributes distinct from $PM_{2\cdot5}$. Since 2000, research into air pollution has frequently addressed both $PM_{2\cdot5}$ and $PM_{2\cdot5}$ absorbance.[21] $PM_{2\cdot5}$ absorbance is highly correlated with measurement of elementary carbon, which is a marker for particles produced by incomplete combustion.[22]

Concentrations of particulate matter, NO_2, and NO_X in outdoor air were modelled in a standardised way in 16 of the 24 study areas (figure 1). In seven areas, only NO_2 and NO_X were modelled, and in one, only particulate matter was modelled (figure 1). Measurements were mostly done between Oct 15, 2008, and Feb 24, 2011, in several sites of each area that were selected to represent spatial variation of air pollution in the residential areas of the participants, allowing development of the LUR models for each pollutant in each study area. However, measurements for the EDEN Nancy cohort were taken in 2002, and for the EDEN Poitiers cohort in 2005. The prediction of LUR models varied between centres and between pollutants.[19,20] Depending on the area, the LUR models explained 60–88% of the variability in the annual average concentrations of $PM_{2\cdot5}$, 50–75% of PM_{10} variability, 87–92% of variability in $PM_{2\cdot5}$ absorbance, 58–90% of NO_2 variability, and 63–88% of NO_X variability (cross-validation R^2).[19,20] Data from routine monitoring stations were used to temporally adjust the LUR estimates to the periods corresponding to each individual pregnancy and trimester of pregnancy.[23]

In addition to LUR-estimated pollutants, we investigated traffic intensity on the nearest road (vehicles per day) and total traffic load (sum of the lengths of each road segment multiplied by the traffic intensity [vehicles per day] on all major roads within 100 m of the residence). We accounted for changes of home address during pregnancy when the date of moving and the new address were available (appendix p 2), except for traffic density, which we analysed only for women who did not change home address during pregnancy.

Detailed information about individual characteristics was obtained during the pregnancy through interviews and self-administrated questionnaires in most cohorts (appendix p 4). We selected adjustment variables a priori (appendix p 19):[2] gestational age (not rounded; continuous and quadratic terms), sex, parity (0, 1, 2, and more), maternal height, weight before pregnancy (broken stick model with a knot at 60 kg), mean number of cigarettes smoked per day during second trimester of gestation, maternal age, maternal education (cohort-specific definitions of low, middle, and high), and season of conception (January–March, April–June, July–September, or October–December). We further adjusted models with traffic indicators for background NO$_2$ concentration. Because air pollution can affect early intrauterine growth, gestational age should preferably be defined from the last menstrual period rather than from early measures of fetal growth.[24] Therefore, gestational age was estimated as the interval between the start of the last menstrual period and delivery when possible (62% of births). Ultrasound-based estimation (16%) was used only when date of last menstrual period was unavailable. When estimates based on last menstrual period or ultrasound were not possible, we used obstetrician estimates (22%). In cohorts for which trimester-specific data for maternal smoking were available, the association with birthweight (and thus presumably the potential for confounding) was strongest for the second and third trimester smoking variables (appendix p 7).

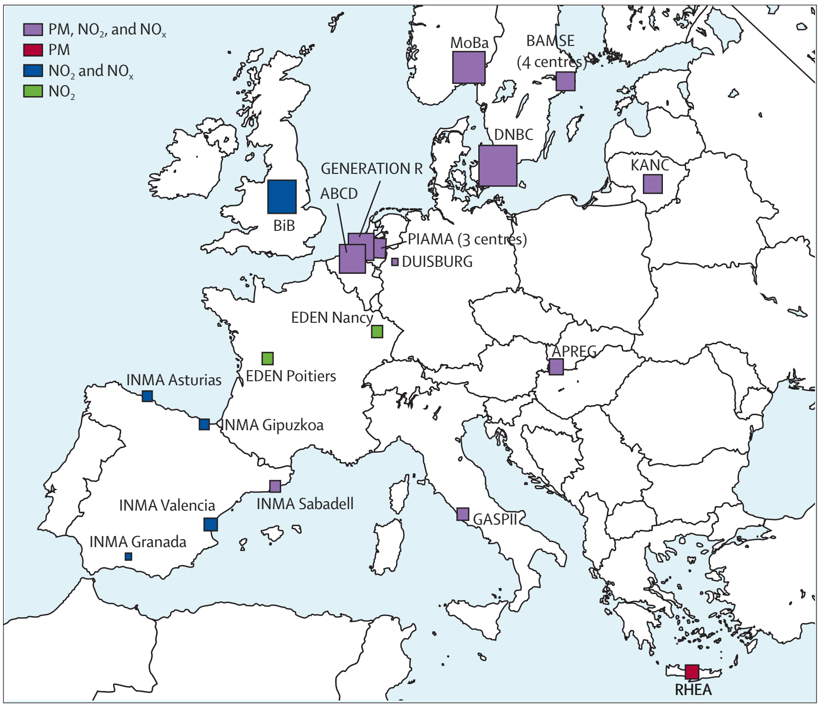

Figure 1: **Location of birth cohorts**

The size of the square indicates the size of the cohort. PM=particulate matter. NO$_2$=nitrogen dioxide. NO$_x$=nitrogen oxides. MoBa=Norwegian Mother and Child Cohort Study. BAMSE=Child, Allergy, Environment, Stockholm, Epidemiology Study. DNBC=Danish National Birth Cohort. BiB=Born in Bradford study. KANC=Kaunus Neonatal Cohort. PIAMA=Prevention and Incidence of Asthma and Mite Allergy birth cohort study. ABCD=Amsterdam-Born Children and their Development study. EDEN=Étude des Déterminants Pré et Postnatals du Développement et de la Santé de l'Enfant. APREG=Air Pollution and Pregnancy Outcomes. INMA=Infancia y Medio Ambiente study. GASPII=Genetica e Ambiente: Studio Prospettico dell'Infanzia in Italia. RHEA=Mother–Child Cohort in Crete.

Statistical analysis

We used logistic regression models to produce odds ratios (ORs) and their 95% CIs for associations between exposure to air pollution and low birthweight at term. We used linear regression models for birthweight and birth head circumference. We restricted analysis of birthweight to term births, because residual plots showed deviation from the models assumptions when preterm deliveries were included (appendix p 20). We analysed birth head circumference for all births. We did pooled analyses using mixed models, including a random effect for centre. Each variable specific to exposure and exposure window was first entered as a continuous variable separately in regression models. We then implemented two-pollutant models. Additionally we did random-effect meta-analyses by centre.

We did several sensitivity analyses. First, we restricted analyses of women with full residential history to those who did not change home address during pregnancy (assuming that residential mobility could result in exposure misclassification). Second, we restricted analyses to areas where exposure models had the highest predictive value (defined as a cross-validation R^2 of more than 0·6). Third, we restricted analyses to one pregnancy per woman, excluding pregnancies other than the first in women with more than one pregnancy during the study period. Fourth, we restricted analyses of birth head circumference to term deliveries. Fifth, we made further adjustment for whether the mother had been born in or had the nationality of the country of the cohort and self-reported maternal exposure to second-hand smoke during pregnancy (only available in a subpopulation). Finally, we did analyses stratified by sex, parity (0, 1, and more), maternal active smoking (no or yes), and maternal education (low, middle, high) to examine potential effect measure modification.

We estimated the population attributable risk of low birthweight at term as the percentage of cases that would be averted within the population if PM$_{2.5}$ pregnancy concentrations were reduced to 10 $\mu g/m^3$—the WHO yearly air quality guideline value.[25] We checked that the risk ratio associated with exposure was equivalent to the OR, because low birthweight at term is a rare outcome.

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See **Online** for appendix

We also calculated the number of cases of low birthweight at term that could be avoided if pregnancy exposure to $PM_{2\cdot5}$ was reduced to 10 μg/m³ in all study areas. We used the formula $NA_m = n_m \times (RR_{m-10} - 1) / RR_{m-10}$,[26] where RR_{m-10} is the adjusted relative risk (RR) of low birthweight at term comparing women exposed to m and those exposed to 10 μg/m³, and n_m is the number of cases of low birthweight at term in the population with an exposure level m. For comparison, we also calculated the population attributable risk corresponding to maternal active smoking.

We used Stata SE (version 12.1) and chose an α of 5% (two tailed).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Mothers were predominately born in the country of their cohort, were non-smokers, and had a mean age of 30 years (table 1, appendix p 8). About 85% of women for whom information about change of address was available did not change address during pregnancy (table 1). Mean gestational age was almost 40 weeks (table 1). 3627 (4·9%) of the 74 178 births were preterm. 3087 infants (4·2%) had low birthweight.

	Pooled cohort (n=74 178)
Country	
Norway	11 183 (15·1%)
Sweden	3868 (5·2%)
Denmark	17 577 (23·7%)
Lithuania	4101 (5·5%)
England	10 709 (14·4%)
Netherlands	19 498 (26·3%)
Germany	194 (0·3%)
France	1281 (1·7%)
Hungary	1290 (1·7%)
Italy	684 (0·9%)
Spain	2623 (3·5%)
Greece	1170 (1·6%)
Maternal nationality (n=72 435)	
Born in country of cohort	57 186 (78·9%)
Born elsewhere	15 249 (21·1%)
Maternal age (years; n=74 101)	30·0 (21·5–38·0)
Maternal education (n=70 878)	
Low	14 207 (20·0%)
Middle	26 515 (37·4%)
High	30 156 (42·6%)
Parity (n=73 560)	
0	38 091 (51·8%)
1	24 427 (33·2%)
>1	11 042 (15·0%)
Maternal height (cm; n=72 739)	166·9 (155·0–178·0)
Maternal weight before pregnancy (kg; n=70 463)	66·6 (50·0–91·0)
Maternal active smoking (n=71 840)	0·8 (0·0–6·0)
No	61 933 (86·2%)
Yes	9907 (13·8%)
Number of cigarettes per day	5·7 (0·4–15·0)
Maternal pregnancy exposure to second-hand smoke (n=69 163)	
No	43 506 (62·9%)
Yes	25 657 (37·1%)
Moved home during pregnancy (n=61 509)	
No	52 552 (85·4%)
Yes	8957 (14·6%)
Season of conception	
January–March	17 324 (23·4%)
April–June	16 697 (22·5%)
July–September	18 939 (25·5%)
October–December	21 218 (28·6%)
Sex of infant	
Boy	37 608 (50·7%)
Girl	36 570 (49·3%)
Gestational age (weeks)	39·8 (37·0–42·0)
Birthweight (g)	3452 (2560–4315)
Term births	70 551 (95·1%)
Low birthweight at term*	1257 (1·8%)
Birth head circumference (cm; n=53 302)	34·8 (32·0–37·0)
$PM_{2\cdot5}$ concentration during pregnancy (μg/m³; n=58 134)	16·5 (8·8–24·9)
$PM_{2\cdot5-10}$ concentration during pregnancy (μg/m³; n=56 704)	9·1 (2·1–16·0)
PM_{10} concentration during pregnancy (μg/m³; n=58 134)	25·4 (11·6–39·4)
$PM_{2\cdot5}$ absorbance during pregnancy (10^{-5} per m; n=58 941)	1·7 (0·9–2·6)
NO_2 concentration during pregnancy (μg/m³; n=72 166)	26·2 (11·7–45·8)
NO_x concentration during pregnancy (μg/m³; n=70 834)	45·5 (15·4–91·1)
Traffic density on nearest street (vehicles per day; n=69 550)	2840 (130–15 439)
Traffic load on major road within 100 m (sum of lengths of each road segment multiplied by traffic intensity [vehicles per day]; n=70 851)	1486 (0–5866)

Data are n (%) or mean (5–95 centiles). $PM_{2\cdot5}$=particulate matter with aerodynamic diameter <2·5 μm. $PM_{2\cdot5-10}$=particulate matter with aerodynamic diameter 2·5–10 μm. PM_{10}=particulate matter with aerodynamic diameter <10 μm. NO_2=nitrogen dioxide. NO_x=nitrogen oxides. *<2500 g after at least 37 weeks' gestation.

Table 1: **Characteristics of the study population**

PM$_{2\cdot5}$ and PM$_{10}$ concentrations were lower in northern areas than in central and southern areas (figure 2, appendix p 21). The correlations between concentrations of different pollutants during pregnancy were modest to high (appendix p 10).

Risk of low birthweight at term was significantly associated with mean pregnancy exposure to PM$_{2\cdot5}$, PM$_{10}$, NO$_2$ (with pooled data from all areas), and traffic density (table 2). The OR for the association between NO$_2$ and low birthweight at term only in areas where PM$_{2\cdot5}$ concentrations were also available decreased when adjusted for PM$_{2\cdot5}$ concentrations (table 2). The association between PM$_{2\cdot5}$ and low birthweight at term was hardly changed by adjustment for NO$_2$ (table 2). The association between low birthweight at term and PM$_{2\cdot5}$ remained significant when we restricted the population to women exposed to mean PM$_{2\cdot5}$ concentrations of less than 25, 20, or 15 μg/m³ during pregnancy (table 3).

The association between PM$_{2\cdot5}$ and low birthweight at term was stronger for women who gave birth to boys than those who had girls, for women who smoked than in those who did not, and in women of low or medium education than in those of high education (table 4). However, these differences were not significant ($p_{\text{interaction}}>0\cdot1$ for all). After restriction to the 25 313 women for whom gestational age was estimated both with ultrasound and from last menstrual period, the association was slightly stronger with the definition based on last menstrual period (adjusted OR 1·15, 95% CI 0·87–1·52) than when the ultrasound-based definition was used (1·10, 0·97–1·13).

Trimester-specific exposures were highly correlated, which restricted identification of crucial windows of exposure and susceptibility. Generally, the point estimates of ORs were fairly similar in most exposure windows (appendix p 11). The combined effect estimates from random-effect meta-analyses were generally similar to those from the adjusted pooled analysis, and we recorded no important heterogeneity between centres in meta-analyses (appendix p 11).

The population attributable risk estimated for a reduction in PM$_{2\cdot5}$ concentration to 10 μg/m³ during pregnancy corresponded to a decrease of 22% (95% CI 8–33%) in cases of low birthweight at term—ie, 145 (57–223) fewer cases of low birthweight at term in a total of 50 151 term babies. By comparison, the adjusted RR for the association between low birthweight at term and maternal active smoking was 2·26 (1·89–2·69), and the proportion of cases of low birthweight at term attributable to maternal active smoking in the population for whom PM$_{2\cdot5}$ data were available was 14% (10–17%). Because ambient air pollution exposure affects more women than active smoking does (45 430 [91%] of 50 151 women exposed to PM$_{2\cdot5}$ concentration of more than 10 μg/m³ *vs* 6237 [12%] who actively smoked), and had a weaker individual effect, the two population attributable risks were similar in size.

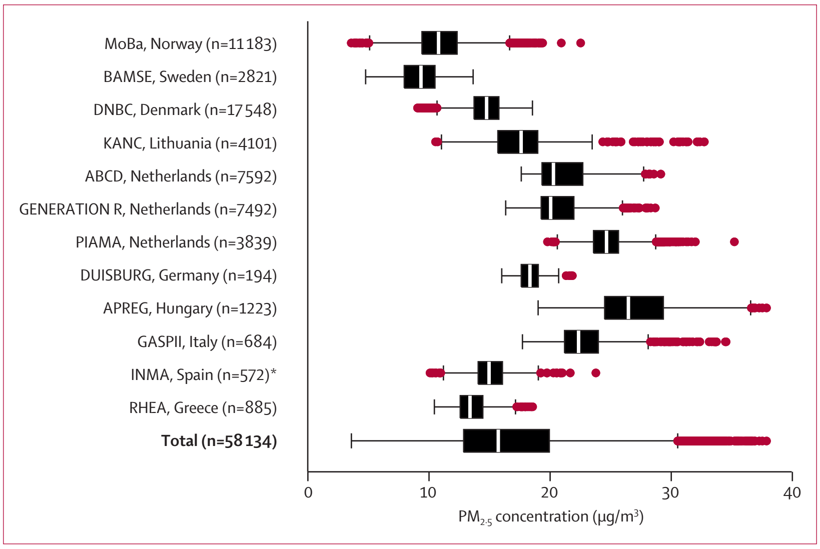

Figure 2: **PM$_{2\cdot5}$ concentrations in the ambient air during pregnancy by cohort and overall**
White lines indicate median, black boxes IQR, horizontal bars the variability outside the upper and lower quartiles (ie, within 1·5 IQR of the lower and upper quartiles), and red circles outliers. Data not available for BiB or EDEN cohorts and four of five INMA centres. PM$_{2\cdot5}$=particulate matter with aerodynamic diameter <2·5 μm. *Data only available for INMA Sabadell.

All pollutants seemed to reduce birthweight for term births, with the exception of traffic density, but none of the associations were significant (table 5). We noted no strong sign of between-centre heterogeneity for PM$_{2\cdot5}$, PM$_{2\cdot5\text{–}10}$, PM$_{10}$, PM$_{2\cdot5}$ absorbance, and traffic indicators in association with birthweight (appendix p 12). Significant reductions in term birthweight were recorded in both unadjusted and adjusted models for PM$_{2\cdot5}$ absorbance exposure during the third trimester and for full pregnancy exposure, and exposure to PM$_{2\cdot5}$, PM$_{2\cdot5\text{–}10}$, and PM$_{10}$ during the third trimester. Associations were also recorded during all exposure periods for NO$_2$ and NO$_X$ in unadjusted models (appendix p 12).

In adjusted models, concentrations of all pollutants and traffic density were associated with reductions in birth head circumference (table 5, appendix p 13). We recorded reductions in head circumference with each 5 μg/m³ increase in PM$_{2\cdot5}$ only in women exposed to PM$_{2\cdot5}$ concentrations of less than 20 μg/m³, but not in those exposed to concentrations of less than 15 μg/m³ (appendix p 14). Adjusted random-effect meta-analyses of birth head circumference showed significant heterogeneity between centres for all pollutants, but not for the traffic indicators (appendix p 13). Overall, in terms of estimated reduction in both birthweight and birth head circumference, the combined effect estimates from the random-effect meta-analyses were smaller than were those from the pooled analyses (appendix p 13).

We noted significantly stronger associations with PM$_{2\cdot5}$ concentrations in women who had not moved than in the whole study population for birthweight (change –13 g [–24 to –1] *vs* –9 g [95% CI –18 to 0]) and birth head circumference (change –0·17 cm [–0·23 to –0·11] *vs*

	Total number with term birth*	Number with low birthweight at term	Odds ratio (95% CI)
One-pollutant models†			
$PM_{2\cdot5}$	50 151	675	1·18 (1·06–1·33)
$PM_{2\cdot5\text{–}10}$	48 995	666	1·01 (0·88–1·15)
PM_{10}	50 151	675	1·16 (1·00–1·35)
$PM_{2\cdot5}$ absorbance	50 835	679	1·17 (0·95–1·39)
NO_2 in areas with $PM_{2\cdot5}$	49 285	656	1·05 (0·95–1·16)
NO_2 in all areas	61 452	1074	1·09 (1·00–1·19)
NO_x in all areas	60 254	1046	1·04 (0·97–1·11)
Traffic density on nearest street	59 030	1000	1·06 (1·01–1·11)
Traffic load on major road within 100 m	60 254	1039	1·01 (0·96–1·07)
Two-pollutant models‡			
$PM_{2\cdot5}$ adjusted for $PM_{2\cdot5\text{–}10}$	48 995	666	1·20 (1·07–1·35)
$PM_{2\cdot5}$ adjusted for $PM_{2\cdot5}$ absorbance	49 931	670	1·18 (1·03–1·36)
$PM_{2\cdot5}$ adjusted for NO_2	49 285	656	1·18 (1·04–1·33)
$PM_{2\cdot5\text{–}10}$ adjusted for $PM_{2\cdot5}$	48 995	666	0·93 (0·81–1·06)
$PM_{2\cdot5\text{–}10}$ adjusted for NO_2	48 134	647	1·02 (0·85–1·22)
PM_{10} adjusted for $PM_{2\cdot5}$ absorbance	49 931	670	1·12 (0·93–1·35)
PM_{10} adjusted for NO_2	49 285	656	1·19 (1·00–1·42)
$PM_{2\cdot5}$ absorbance adjusted for $PM_{2\cdot5}$	49 931	670	0·99 (0·79–1·24)
$PM_{2\cdot5}$ absorbance adjusted for $PM_{2\cdot5\text{–}10}$	48 776	661	1·20 (0·97–1·48)
$PM_{2\cdot5}$ absorbance adjusted for NO_2	50 136	664	1·12 (0·87–1·46)
NO_2 adjusted for $PM_{2\cdot5}$	49 285	656	1·01 (0·91–1·11)
NO_2 adjusted for $PM_{2\cdot5\text{–}10}$	48 134	647	1·04 (0·92–1·17)
NO_2 adjusted for $PM_{2\cdot5}$ absorbance	50 136	664	1·01 (0·88–1·15)

All effect estimates correspond to an increase of 5 μg/m³ in personal exposure level for $PM_{2\cdot5}$ and $PM_{2\cdot5\text{–}10}$, 10 μg/m³ for PM_{10}, 10^{-5} per m for $PM_{2\cdot5}$ absorbance, 10 μg/m³ for NO_2, 20 μg/m³ for NO_x, 5000 vehicles per day for traffic density, and 4 000 000 vehicles per day×m for traffic load. $PM_{2\cdot5}$=particulate matter with aerodynamic diameter <2·5 μm. $PM_{2\cdot5\text{–}10}$=particulate matter with aerodynamic diameter 2·5–10 μm. PM_{10}=particulate matter with aerodynamic diameter <10 μm. NO_2=nitrogen dioxide. NO_x=nitrogen oxides. *Number of women who gave birth at term for whom data for all adjustment variables and indicated exposure are available. †Effect of pregnancy mean exposure to air pollutants on low birthweight at term estimated in pooled analyses using logistic regression with random effect of centre adjusted for gestational age (weeks and [weeks]²), sex, parity (0, 1, 2, or more), maternal height, weight before pregnancy (broken stick model with a knot at 60 kg), maternal active smoking during second trimester (cigarettes per day), maternal age, maternal education (low, middle, high), and season of conception (January–March, April–June, July–September, October–December). Traffic density on nearest street and traffic load models were further adjusted for background concentrations of NO_2. ‡Further adjusted for the indicated pollutant.

Table 2: **Associations of ambient air pollution during pregnancy with low birthweight at term**

	Total number with term birth*	Number with low birthweight at term	Odds ratio (95% CI)
Exposed to <15 μg/m³	21 575	235	1·79 (1·29–2·48)
Exposed to <20 μg/m³	38 017	477	1·41 (1·20–1·65)
Exposed to <25 μg/m³	47 737	637	1·21 (1·06–1·38)
None	50 151	675	1·18 (1·06–1·33)

All effect estimates correspond to an increase of 5 μg/m³ in pregnancy mean exposure to $PM_{2\cdot5}$. Estimated in pooled analyses using logistic regression with random effect of centre adjusted for gestational age (weeks and [weeks]²), sex, parity (0, 1, 2, or more), maternal height, weight before pregnancy (broken stick model with a knot at 60 kg), maternal active smoking during second trimester (cigarettes per day), maternal age, maternal education (low, middle, high), and season of conception (January–March, April–June, July–September, October–December). Participating women exposed to <15 μg/m³ are from MOBA, BAMSE, DNCB, KANC, INMA Sabadell, and RHEA cohorts. Participating women exposed to <20 μg/m³ are also from ABCD, GENERATION R, DUISBURG, APREG, and GASPII cohorts. Participating women exposed to <25 μg/m³ are also from the PIAMA cohort. *Number of women who gave birth at term for whom data for all adjustment variables and an exposure estimate for $PM_{2\cdot5}$ during the whole pregnancy are available. $PM_{2\cdot5}$=particulate matter with aerodynamic diameter <2·5 μm.

Table 3: **Associations of $PM_{2\cdot5}$ concentrations during pregnancy with low birthweight at term, restricted to concentrations less than specified values**

–0·08 cm [–0·12 to –0·03]; appendix p 15). Results of the other sensitivity analyses were similar to those of the main analyses (appendix p 15). Maternal active smoking was associated with a significant reduction in birth head circumference when compared with mothers who had not smoked (difference –0·31 cm, 95% CI –0·36 to –0·27; appendix p 16). Maternal exposure to second-hand smoke was not associated with a reduction in head circumference (difference 0·0005, 95% CI –0·04 to 0·04; appendix p 16).

Interaction tests suggested no strong evidence of effect measure modification on head circumference between maternal active smoking (binary coding) and maternal exposure to $PM_{2\cdot5}$ (p=0·50; appendix p 16). For $PM_{2\cdot5}$ absorbance and NO_X, effect measure modification with maternal smoking suggested a larger reduction in birth head circumference in children of smokers than in children of non-smokers (appendix p 15). Information about alcohol consumption during pregnancy was available for about a third of the cohorts (appendix p 17). Few women (<1%) consumed at least one glass of alcohol per day. The reported effect estimates of $PM_{2\cdot5}$ were qualitatively unchanged after further adjustments for alcohol intake (appendix p 17).

Discussion

We have shown that ambient air pollutants—particularly $PM_{2\cdot5}$—and traffic density are associated with increases in risk of low birthweight at term and reductions in birthweight and birth head circumference (panel). Our findings suggest that in-utero exposure to ambient air pollution in European urban areas could explain a substantial proportion of cases of low birthweight at term. We used data from a large population with fairly low exposure levels, and increased risks were recorded in the population exposed to levels below the present European Union annual limit of 25 μg/m³.

The estimated 18% increase in risk of low birthweight at term associated with a 5 μg/m³ increase in exposure to $PM_{2\cdot5}$ in our study (RR 1·18) is larger than that reported in meta-analyses (appendix p 18).[3–5] We recalculated the OR for low birthweight at term from Dadvand and colleagues' study[5] for a 5 μg/m³ increase: 1·02 (95% CI 0·99–1·04), after adjustment for centre-specific covariates. The recalculated OR for Stieb and colleagues' analysis[3] was 1·02 (0·99–1·06). The recalculated decrease in birthweight for this study[3] was 12 g (23 to 1), compared with 7 g in our study. The studies included in the meta-analyses[3–5] were

	Total number with term birth*	Number with low birthweight at term	Odds ratio (95% CI)
Entire study population	50 151	675	1·18 (1·06–1·33)
Women who did not change address	33 927	452	1·15 (0·99–1·33)
Study areas with the land-use regression models of the highest prediction	28 263	393	1·23 (1·06–1·42)
Women who participated once	47 192	655	1·17 (1·05–1·32)
Women for whom data for ethnic origin not missing	49 632	673	1·16 (1·05–1·29)
Additional adjustment for maternal ethnic origin	49 632	673	1·16 (1·05–1·28)
Women for whom data for second-hand smoke not missing	47 583	645	1·09 0·97–1·22)
Additional adjustment for second-hand smoke	47 583	645	1·08 (0·96–1·21)
Boys	25 405	261	1·25 (1·09–1·44)
Girls	24 746	414	1·13 (1·02–1·25)
Primiparous women	23 229	218	1·19 (1·02–1·39)
Mulitiparous women	26 922	457	1·17 (1·06–1·30)
Non-smoking women	43 914	495	1·14 (1·02–1·28)
Smoking women	6237	180	1·26 (1·07–1·48)
Women with low education	6967	144	1·25 (1·03–1·51)
Women with middle education	20 442	284	1·23 (1·10–1·39)
Women with high education	22 742	247	1·10 (0·94–1·28)

Effect estimates from pooled analyses (per 5 $\mu g/m^3$ increase in $PM_{2\cdot5}$) using logistic regression with random effect of centre adjusted for gestational age (weeks and [weeks]^2), sex, parity (0, 1, 2, or more), maternal height, weight before pregnancy (broken stick model with a knot at 60 kg), maternal active smoking during second trimester (cigarettes per day), maternal age, maternal education (low, middle, high), and season of conception (January–March, April–June, July–September, October–December). $PM_{2\cdot5}$ concentrations not available for BiB and EDEN cohorts. *Number of women who gave birth at term for whom data for all adjustment variables and an exposure estimate for $PM_{2\cdot5}$ during the whole pregnancy are available. $PM_{2\cdot5}$=particulate matter with aerodynamic diameter <2·5 μm.

Table 4: **Sensitivity analyses of $PM_{2\cdot5}$ concentrations during pregnancy and low birthweight at term**

heterogeneous in design—eg, the exposure assessment varied from proximity-based or monitoring-based to model-based—and the assessment of potential confounders varied. Part of the heterogeneity noted could also be explained by the different chemical composition of particulate matter in the various study areas.[27]

Low birthweight adjusted for gestational duration is the most frequently studied outcome;[2–8,17] however, as in other studies,[5-7,18] we restricted the analyses of low birthweight to term births as a way to distinguish between babies with low birthweight because of growth restriction and those with low birthweight because of early delivery.[28] Exclusion of preterm births from our analyses of birthweight slightly reduced the sample size and might also have resulted in a reduced variability in birthweight compared with the entire population.

The effects of $PM_{2\cdot5}$ on low birthweight and birth head circumference have not been simultaneously assessed in any previous large studies.[3–7,17,18] Head circumference is an important outcome because of the potential effect of air pollution on neurodevelopment,[29] and because birth head circumference has been associated with intelligence.[30] The effect of $PM_{2\cdot5}$ on head circumference has also not been assessed in previous studies.[31–34] Adverse effects of other air pollutants on head circumference have been reported in two small studies,[31,32] but not in others.[33,34]

	Birthweight*		Birth head circumference	
	Total number of participants	Change in birthweight (g)	Total number of participants	Change in birth head circumference (cm)
$PM_{2\cdot5}$	50 151	–7 (–17 to 2)	34 499	–0·08 (–0·12 to –0·03)
$PM_{2\cdot5–10}$	48 995	–3 (–11 to 6)	33 301	–0·09 (–0·12 to –0·05)
PM_{10}	50 151	–8 (–19 to 3)	34 499	–0·13 (–0·18 to –0·09)
$PM_{2\cdot5}$ absorbance	50 835	–3 (–13 to 7)	35 119	–0·18 (–0·22 to –0·13)
NO_2	61 452	–1 (–6 to 4)	45 446	–0·08 (–0·10 to –0·07)
NO_X	60 254	–1 (–4 to 3)	44 207	–0·06 (–0·07 to –0·05)
Traffic density on nearest street	59 030	2 (–1 to 5)	43 109	–0·02 (–0·03 to –0·01)
Traffic load on major road	60 254	–1 (–4 to 2)	44 371	–0·02 (–0·05 to 0·00)

Data in parentheses are 95% CIs. Effect of pregnancy mean exposure to air pollutants estimated in pooled analyses using linear regression with random effect of centre adjusted for gestational age (weeks and [weeks]^2), sex, parity (0, 1, 2, or more), maternal height, weight before pregnancy (broken stick model with a knot at 60 kg), maternal active smoking during second trimester (cigarettes per day), maternal age, maternal education (low, middle, high), and season of conception (January–March, April–June, July–September, October–December). Traffic density on nearest street and traffic load is further adjusted for background concentration of NO_2. All effect estimates correspond to an increase of 5 $\mu g/m^3$ for $PM_{2\cdot5}$ and $PM_{2\cdot5–10}$, 10 $\mu g/m^3$ for PM_{10}, 10^{-5} per m for $PM_{2\cdot5}$ absorbance, 10 $\mu g/m^3$ for NO_2, 20 $\mu g/m^3$ for NO_X, 5000 vehicles per day for traffic density, and 4 000 000 vehicles per day×m for traffic load. $PM_{2\cdot5}$=particulate matter with aerodynamic diameter <2·5 μm. $PM_{2\cdot5–10}$=particulate matter with aerodynamic diameter 2·5–10 μm. PM_{10}=particulate matter with aerodynamic diameter <10 μm. NO_2=nitrogen dioxide. NO_X=nitrogen oxides. *Analysis restricted to term births (≥37 weeks of gestation).

Table 5: **Associations between birthweight and head circumference with ambient air pollution during pregnancy**

The proportion of cases of low birthweight at term that is attributable to $PM_{2\cdot5}$ exposure in our study population was similar to that attributable to maternal active smoking during pregnancy. The smaller individual effect of $PM_{2\cdot5}$ on low birthweight at term compared with smoking was counterbalanced by the higher prevalence of $PM_{2\cdot5}$ exposure of more than 10 μg/m³ during pregnancy than that of active smoking. In view of the widespread exposure of pregnant women worldwide to ambient air pollution at similar or even higher concentrations than those assessed in our study, further actions towards improving the ambient air quality in residential areas are recommended.

Ambient air contains a dynamic mixture of pollutants, and the mechanisms by which the airborne inhalable particles, metals, or polycyclic aromatic hydrocarbons could affect fetal growth are unknown. Hypotheses are that air pollutants could cause endocrine disruption, alter placental growth, decrease placental exchange of nutrients and gases, or cause oxidative stress—all of which could possibly lead to altered fetal growth.[2,35]

In our study, $PM_{2\cdot5}$, PM_{10}, NO_2, and traffic density were significantly associated with low birthweight at term. The effects of particulate matter were mostly explained by the fine (diameter <2·5 μm) rather than the coarse (2·5–10 μm) fraction. Within-city differences in pregnancy exposure are mostly driven by spatial (rather than temporal) variations. Our finding that within-centre exposure contrasts were related to the risk of low birthweight at term (as shown by the meta-analysis results) shows that local sources are important contributors to the toxic component of the inhaled ambient air and could restrict intrauterine growth.

Panel: Research in context

Systematic review

We searched PubMed for reports published in English before April 20, 2013, with the search terms “air pollution and birthweight”, “air pollution and fetal growth”, “air pollution and intrauterine restriction”, “air pollution and birth head circumference”, and “air pollution and birth outcomes”. We used three reviews and meta-analyses, last updated in January, 2011,[3-5] as the basis of our systematic review. At the time our study began in 2008, some evidence of an association between air pollution and fetal growth restriction was available, but many previous studies had poor exposure assessment, small size of included cohorts, and no or little information about potential confounders. We identified no large studies from European populations exposed to low amounts of air pollution.

Interpretation

We have shown that fine particulate matter air pollution is associated with an increased risk of low birthweight at term and reduced newborn head circumference. Increased risks were recorded at exposure levels well below the present European Union limits. Our study had a large sample, broad European coverage, standardised fine-scale exposure assessment, and adjustment for a wide range of potential confounders. Urban particulate matter air pollution is widespread, and our results suggest that further reductions could reduce the number of cases of low birthweight at term in Europe.

Our study had three important strengths: the standardised, comprehensive exposure assessment; the harmonised and detailed information about potential confounders; and the large population spread throughout a large geographical area. Detailed information about individual characteristics (eg, maternal stature, parity, ethnic origin, education, and active and passive smoking during pregnancy) was prospectively obtained in a way that enabled us to reduce potential biases through adjustment in a large study population.

Parity was the most important confounder, and it was adjusted for a priori. Indeed, all effect estimates increased when models were not adjusted for parity (data not shown). Few women reported frequent alcohol consumption during pregnancy and the effect estimate of $PM_{2\cdot5}$ varied little after further post-hoc adjustment for alcohol consumption of more than one drink per day in the cohorts for which data for alcohol consumption were available, which suggests that confounding by alcohol consumption was not a big concern in our study. Illegal drug use is likely to be infrequent in the pregnant women included in the cohorts, and we do not believe that it was a strong potential confounder. It is unlikely that prescribed drugs that are known to affect fetal growth would have biased our results, because participation of pregnant women with chronic diseases for which drugs are needed during pregnancy is low in cohort studies.

Most of the pregnant women who were included attended prenatal care, because most participants were recruited at the place and time of prenatal care, which is free in most European countries. After adjustment for active smoking, body-mass index, socioeconomic status, and other factors, our data did not suggest that maternal exposure to second-hand smoke during pregnancy confounded the reported results. To our knowledge, no studies have shown an effect of area-level deprivation on birthweight in which individual factors likely to mediate this effect (eg, active or passive smoking, body-mass index, and individual socioeconomic status) have been controlled for, as in our study. Deprivation score was available for only a few cohorts, and accounting for it hardly changed the adjusted effect of $PM_{2\cdot5}$ concentrations on birthweight (data not shown). We adjusted our models for factors such as individual socioeconomic status defined by education and for several variables (eg, smoking, maternal weight, and maternal height) that possibly mediate the effect of deprivation on health.

The harmonisation of international data allowed us to do pooled analyses. We based our conclusions on the powerful pooled analyses, but we also presented results from the meta-analyses, because this approach has been used in most previous multicentre studies of air pollution in which pooling was not possible. Differences between both approaches are expected, if only because the meta-analysis relied on only within-centre exposure contrasts and the pooled analysis made use of within-centre and between-centre exposure contrasts. The point estimates for the effect of $PM_{2\cdot5}$ pregnancy exposure on low birthweight at term were similar for the pooled analyses and the meta-analyses, although the point estimates were attenuated in the meta-analyses when compared with the pooled analysis for birthweight and head circumference. The analyses of low birthweight at term seem to be most robust to model change.

Several pollutants at individual home addresses were assessed in a harmonised manner throughout Europe through LUR modelling using ad-hoc measurement campaigns and detailed data for ambient air quality and road traffic.[19,20] Thus, we could estimate small-scale spatial exposure contrasts during the pregnancy periods. Air pollution measurements to develop LUR models were taken in 2008–11, whereas pregnancies occurred in 1994–2011—a median of 5 years (range 1–14) earlier. All centres had long-term routine monitoring data that meant we could temporally adjust exposure during the exact pregnancy periods. This approach relied on the assumption that the spatial distribution of the determinants of air pollution (eg, traffic, land use, and household density) had not changed substantially. Spatial contrasts have been shown to be stable with time,[36,37] but because we sometimes had to rely on a proxy pollutant to extrapolate back to another one, we recognise the potential for exposure misclassification. Assumptions about similar temporal trends for $PM_{2\cdot5}$ and PM_{10} were made to extrapolate back to $PM_{2\cdot5}$. Our exposure assessment was limited to home address, and exposures elsewhere were not estimated, because detailed information about time-activity patterns or personal measures were not available. Incomplete information about residential mobility could introduce exposure misclassification.[38] However, most women did not move during pregnancy, and analyses restricted to women who did not change home address during pregnancy gave similar results to those reported for the full study population. Confidence intervals were wider in an analysis restricted to non-movers, probably as a result of smaller sample size.

In conclusion, we recorded that exposure to ambient air pollution in pregnancy at levels currently reported in Europe is associated with reduced fetal growth. Our findings suggest that a substantial proportion of cases of low birthweight at term could be prevented in Europe if urban air pollution—particularly $PM_{2\cdot5}$—was reduced.

Contributors

MP, JL, EP, MJN, GP, BB, MKog, and RS conceived and planned the study. MP analysed data, reviewed previous reports, interpreted findings, and wrote the first draft of the report. MP, LG-A, CB, and RS harmonised and pooled data and created the variables. LG-A, IA, RMJB, MC, ADe, GH, KdH, SEH, WN, OR-N, ES, MJN, BB, and RS contributed to the air pollution assessment. LG-A contributed to statistical analyses and did the back-extrapolation of exposure. A-MNA, FB, LC, MvE, FF, UG, RG, BH, SEH, VWVJ, CK, MKor, UK, PN, WN, DPor, DPos, PR, JS, MJV, TGMV, AW, JW, MKog, and RS designed the cohort study, obtained funding, managed the cohort, and collected data from the cohort's participants. ADa, ADe, ME, AF-S, MFF, UG, EHvdH, RG, OG, UK, AL, JL, EP, DPor, DPos, MS, DT, MJV, TGMV, MW, and MJV collected data. MJN, MKog, and RS supervised the analysis and contributed to the writing of the report. All authors contributed to critical reading of the report, interpreted data, and approved the report for publication.

Conflicts of interest

We declare that we have no conflicts of interest.

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