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Original Contribution

The Influence of Meteorological Factors and Atmospheric Pollutants on the Risk of Preterm Birth

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Atmospheric pollutants and meteorological conditions are suspected to be causes of preterm birth. We aimed to characterize their possible association with the risk of preterm birth (defined as birth occurring before 37 completed gestational weeks). We pooled individual data from 13 birth cohorts in 11 European countries (71,493 births from the period 1994–2011, European Study of Cohorts for Air Pollution Effects (ESCAPE)). City-specific meteorological data from routine monitors were averaged over time windows spanning from 1 week to the whole pregnancy. Atmospheric pollution measurements (nitrogen oxides and particulate matter) were combined with data from permanent monitors and land-use data into seasonally adjusted land-use regression models. Preterm birth risks associated with air pollution and meteorological factors were estimated using adjusted discrete-time Cox models. The frequency of preterm birth was 5.0%. Preterm birth risk tended to increase with first-trimester average atmospheric pressure (odds ratio per 5-mbar increase = 1.06, 95% confidence interval: 1.01, 1.11), which could not be distinguished from altitude. There was also some evidence of an increase in preterm birth risk with first-trimester average temperature in the −5°C to 15°C range, with a plateau afterwards (spline coding, *P* = 0.08). No evidence of adverse association with atmospheric pollutants was observed. Our study lends support for an increase in preterm birth risk with atmospheric pressure.

atmospheric pollution; atmospheric pressure; cohort studies; humidity; meteorological conditions; pooled analysis; preterm birth; temperature

Abbreviations: ABCD, Amsterdam Born Children and Their Development; APREG, Air Pollution and Pregnancy Outcomes; BAMSE, Barn, Allergi, Miljö, Stockholm, Epidemiologi; BiB, Born in Bradford; CI, confidence interval; DNBC, Danish National Birth Cohort; EDEN, Étude des Déterminants Pré et Post Natals du Développement et de la Santé de l'Enfant; ESCAPE, European Study of Cohorts for Air Pollution Effects; GASPII, Genetica e Ambiente: Studio Prospettico dell'Infanzia in Italia; INMA, Infancia y Medio Ambiente; KANC, Kaunas Neonatal Cohort; MoBa, Den Norske Mor og Barn-Undersøkelsen; OR, odds ratio; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; PM_{10}, particulate matter with an aerodynamic diameter less than or equal to 10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; RHEA, Rhea Mother-Child Study.

Editor's note: *An invited commentary on this article appears on page 259, and the authors' response appears on page 262.*

Preterm birth is the adverse pregnancy outcome entailing the largest health burden in the short and long terms (1). In addition to maternal smoking (2), suspected modifiable risk factors include exposure to phthalate esters (3), atmospheric pollutants (4, 5), and meteorological conditions (6–9).

Previous studies that found a detrimental association between air pollution and preterm birth (4, 5) relied on various designs, such as birth-records–based cohort studies (10–12), time-series analyses (13, 14), case-control studies (15), and a natural experiment (16). Many of these studies were conducted in the United States, where the incidence of preterm delivery is approximately twice as high as in Western Europe and may thus have a different etiology. Very few of these studies relied on cohorts, which allow efficient control for confounders, and few of the cohort studies used survival modeling (17), which is an appropriate way to characterize associations of time-varying exposures with survival outcomes (18, 19).

Previously, researchers have also suggested short-term associations of temperature with preterm birth risk (6–9). Investigators have rarely considered atmospheric pressure or exposure windows of a trimester or more. Meteorological factors have a strong influence on daily air pollution levels, and this can confound any association between atmospheric pollutants and preterm birth risk. Few studies of associations between air pollutants and preterm birth have included corrections for meteorological factors (11, 20).

Our aim was to characterize the association of atmospheric pollutants and meteorological factors with preterm birth in European cohorts. Our a priori hypotheses were that atmospheric pollutants could have a (monotonic) influence on preterm birth risk and that temperature could influence preterm birth risk, possibly in a nonmonotonic way.

METHODS

Study population

We focused on cohorts of pregnant women and newborns included in the European Study of Cohorts for Air Pollution Effects (ESCAPE), described elsewhere (21, 22). The Duisburg cohort was not considered here because women with preterm births had not been recruited at that site, so it was not eligible for this study. We included 13 cohorts from 11 European countries (Amsterdam Born Children and Their Development (ABCD), Amsterdam, the Netherlands; Air Pollution and Pregnancy Outcomes (APREG), Gyor, Hungary; Barn, Allergi, Miljö, Stockholm, Epidemiologi (BAMSE), Stockholm area, Sweden; Born in Bradford (BiB), Bradford, England; Danish National Birth Cohort (DNBC), Copenhagen area, Denmark; Étude des Déterminants Pré et Post Natals du Développement et de la Santé de l'Enfant (EDEN), Nancy and Poitiers, France; Genetica e Ambiente: Studio Prospettico dell'Infanzia in Italia (GASPII), Rome, Italy; Generation R, Rotterdam, the Netherlands; Infancia y Medio Ambiente (INMA), 5 centers in Spain; Kaunas Neonatal Cohort (KANC), Kaunas, Lithuania; Den Norske Mor og Barn-Undersøkelsen (MoBa), Oslo area, Norway; Prevention and Incidence of Asthma and Mite Allergy (PIAMA), 3 regional centers in the Netherlands; and Rhea Mother-Child Study (RHEA), Heraklion, Greece; Figure 1). Recruitment periods spanned 1994–2010. To be included, women had to have delivered a live infant and to have resided during pregnancy in an area where air pollution models had been developed as part of the ESCAPE project. Data were transferred to Institut National de la Santé et de la Recherche Médicale (INSERM, Grenoble, France), where they were harmonized and pooled (21). We included only singleton newborns. When women had several pregnancies during the study period, we included only the first.

Health outcome

Preterm births (births occurring before 37 completed weeks of gestation) were identified by the gestational duration, based whenever possible on date of conception as estimated from the last menstrual period (23). For 38% of births, we used, by order of decreasing preference, the ultrasound-based estimate or gestational duration from birth records. When the discrepancy between last menstrual period–based gestational duration (or the information from birth records) and the ultrasound-based estimate was 3 weeks or more, we modified values, assuming the ultrasound-based estimate was correct. Information on cesarean delivery was not available for all cohorts. In sensitivity analyses, we focused on cohorts in which information on the occurrence of a cesarean delivery was available (excluding the ABCD, APREG, and KANC cohorts), and we repeated analyses excluding pregnancies ending with a planned cesarean delivery or for which information on whether the cesarean delivery was planned was missing.

Exposure assessment

Meteorological parameters. Outdoor temperature, humidity, and atmospheric pressure at the altitude of the city were defined from the hourly measures of a single monitoring station at each study center and averaged during several temporal windows. Data on atmospheric pressure were not available for the KANC cohort. The exposure windows considered were the first trimester of pregnancy (from day 14—counting from the last menstrual period—to day 105) and the second trimester of pregnancy (from day 106 to day 197), as well as 1-week, 4-week, and whole-pregnancy exposure windows (see "Statistical modeling," below). Exposure levels after gestational week 37 (after the study outcome) were not considered. Exposures incurred during the third trimester, a period during which (preterm) deliveries occur, were considered only through the analyses for the 1- and 4-week exposure windows.

Air pollution and traffic indicators. Land-use regression models have been developed (24, 25), allowing estimation of annual mean concentrations of ambient particulate matter with an aerodynamic diameter less than or equal to 2.5 µm ($PM_{2.5}$) or 10 µm (PM_{10}), coarse particulate matter ($PM_{2.5-10}$),

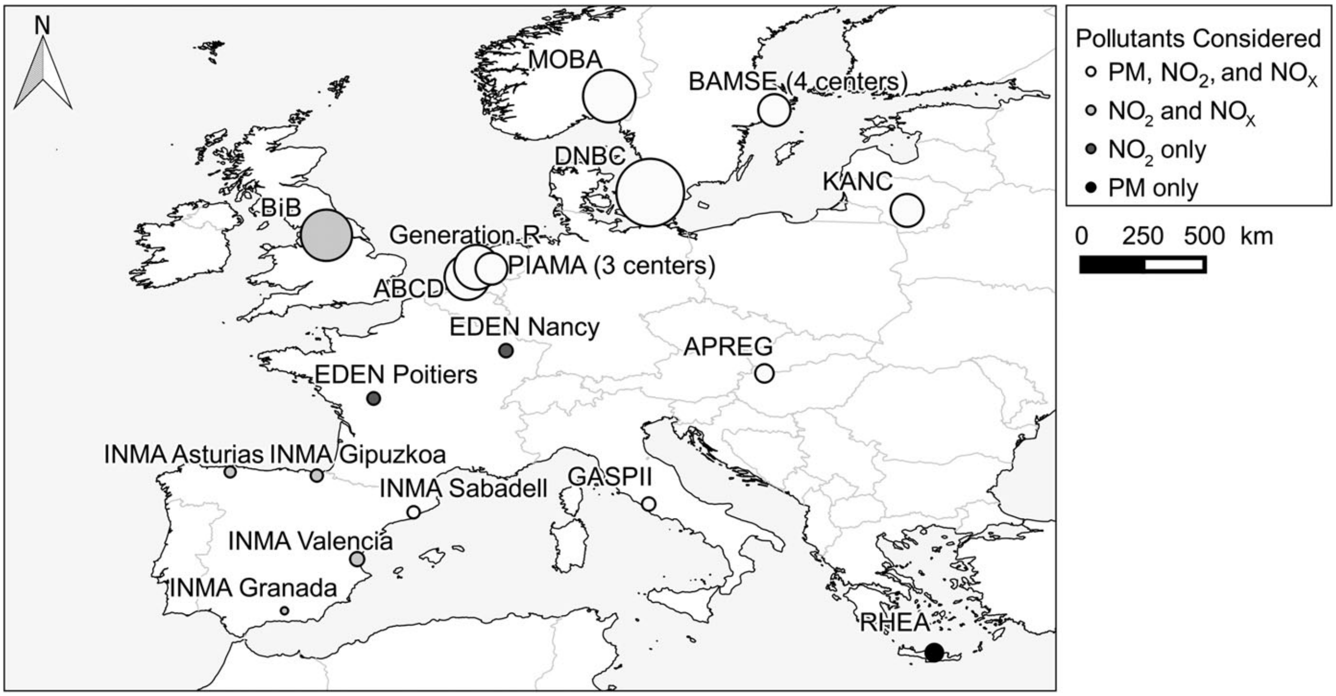

Figure 1. Locations of the study areas within Europe and pollutants assessed at each location, 13 cohorts in the European Study of Cohorts for Air Pollution Effects, 1994–2010. The surface of the circle is proportional to the number of subjects at each study center. ABCD, Amsterdam Born Children and Their Development; APREG, Air Pollution and Pregnancy Outcomes; BAMSE, Barn, Allergi, Miljö, Stockholm, Epidemiologi; BiB, Born in Bradford; DNBC, Danish National Birth Cohort; EDEN, Étude des Déterminants Pré et Post Natals du Développement et de la Santé de l'Enfant; GASPII, Genetica e Ambiente: Studio Prospettico dell'Infanzia in Italia; INMA, Infancia y Medio Ambiente; KANC, Kaunas Neonatal Cohort; MOBA, Den Norske Mor og Barn-Undersøkelsen; NO_x, nitrogen oxides; NO_2, nitrogen dioxide; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; PM, particulate matter; RHEA, Rhea Mother-Child Study.

$PM_{2.5}$ absorbance (a proxy of black carbon particulate-matter content), nitrogen dioxide, and nitrogen oxides at each mother's home address. For budgetary reasons, particulate-matter levels were assessed in a subgroup of cohorts (Figure 1). Exposure corresponded to the time-weighted average of exposure at all addresses during the exposure window considered (if information on changes of address was available) or to the address at inclusion or birth (when information on successive addresses had not been collected). We performed sensitivity analyses restricted to women who had not changed their home addresses during pregnancy (or for whom all addresses were known) in the subgroup of cohorts for which this information was available.

Land-use regression models were temporally adjusted using an approach relying on city-specific routine monitoring stations, allowing us to obtain estimates of exposure relevant to each exposure window (21, 26, 27). Traffic density on the street nearest to the maternal home address and total traffic load on major roads within a 100-m distance were also estimated (21).

Statistical modeling

Unless otherwise specified, analyses were conducted using pooled data from all the cohorts. The associations of first- and second-trimester exposures with preterm birth risk were assessed in distinct adjusted logistic regression models with a random effect for study center (STATA, version 12 (xtlogit function); StataCorp LP, College Station, Texas). Studying the association between exposures whose value may change with the duration of the pregnancy and preterm birth risk requires survival modeling (18, 19). For week-specific, month-specific, and whole-pregnancy exposures, we used a discrete-time Cox model (logistic link) with birth (censored at 37 gestational weeks) as the outcome and week as the discrete-time variable. Time-varying exposures (meteorological conditions and air pollutants) allowed us to characterize the adjusted association between the risk of birth in a given week (before 37 gestational weeks) and exposure in the previous week, month, or duration since conception (whole-pregnancy exposure). We compared the shapes of the associations between whole-pregnancy temperature averages and preterm birth risk estimated using both our discrete-time Cox model and a logistic model. The logistic model was unable to accommodate time-varying exposures in the context of at-risk periods differing between cases and noncases (i.e., term births), possibly leading to bias.

Adjustment factors. For air pollution estimates, we reported the estimates from unadjusted models with a random effect for the study center (model 1), a model that adjusted for all a priori selected potential confounders excluding meteorological factors (model 2), and a model that adjusted for all a priori selected potential confounders including meteorological factors (model 3). We adjusted for meteorological factors using the time window in which their association with the outcome was strongest (which was not necessarily the same as the window considered for atmospheric pollutants). Air pollution levels were coded using continuous variables, and estimates were reported for a priori–defined increments (21). Models for meteorological factors were not adjusted for air pollutants, which we considered to be possible consequences of meteorological conditions. We used restricted cubic-spline coding (28) for meteorological parameters, and we tested deviation from linearity through a likelihood test. When there was no evidence of deviation from linearity, we additionally used a linear coding of meteorological factors; in the case of a V-shaped relationship, we used a broken-stick (i.e., piecewise linear) coding (29) with a single knot located at the apparent change in slope. Center-specific analyses with subsequent random-effect meta-analyses were conducted as sensitivity analyses, as were analyses focusing on very preterm birth risk (risk of birth before 32 completed weeks of gestation).

RESULTS

Study population

Preterm birth prevalence was 5.0% (3,533 of 71,493 births), ranging from 3.9% (Copenhagen, Denmark) to 12.7% (Heraklion, Greece; Table 1). Adjusted odds ratios for preterm birth, comparing mothers who smoked during the second trimester of pregnancy with women who did not smoke, were 1.3 (95% confidence interval (CI): 1.1, 1.4) for women smoking 1–5 cigarettes per day, 1.3 (95% CI: 1.1, 1.6) for women smoking 6–10 cigarettes per day, and 1.6 (95% CI: 1.2, 2.0) for women smoking more than 10 cigarettes per day.

Meteorological factors and preterm birth

The distributions of meteorological variables are shown in Table 1 and Web Figures 1A–1C (available at http://aje.oxfordjournals.org/), and their correlations are shown in Web Table 1. Between-city variations explained 15%, 48%, and 95% of the variability in first-trimester temperature, humidity, and pressure, respectively.

Adjusted restricted cubic-spline models were not strongly in favor of an association between temperature and preterm birth risk (Web Figure 2). The exposure window with the strongest association was the first trimester of pregnancy ($P = 0.08$). Preterm birth risk tended to increase when first-trimester temperature increased from −5°C to approximately 10°C (Web Figure 2B). A broken-stick coding with a knot at 10°C yielded adjusted odds ratios for preterm birth of 1.03 per 1°C increase in first-trimester temperatures below 10°C (95% CI: 1.01, 1.04) and 0.99 per 1°C increase above 10°C (95% CI: 0.97, 1.01). Meta-analytical results were similar (Web Figure 3). When first-trimester temperature was coded in categories, the odds ratios for preterm birth were 1.13 (95% CI: 1.00, 1.27), 1.14 (0.99, 1.33), and 1.20 (0.99, 1.45) for temperatures in the 5°C–9.9°C, 10°C–14.9°C, and ≥15°C ranges, respectively; temperatures below 5°C were the referent (P for trend = 0.08).

Associations between whole-pregnancy temperature and risk of preterm birth estimated with a survival model were weak ($P = 0.45$), had an inverse U-shape, and strongly differed from estimates of a logistic model, which were U-shaped and stronger ($P < 0.005$), a manifestation of a bias in the logistic modeling approach (Web Figure 4).

There was no evidence of an association between humidity and preterm birth risk for any time window considered ($P > 0.20$, Web Figure 5).

The time window corresponding to the strongest association of atmospheric pressure with preterm delivery was the first trimester of pregnancy (Web Figure 6). The association corresponded to a monotonic increase (Figure 2; test of deviation from linearity, $P = 0.20$). The odds ratio for preterm delivery was 1.06 per 5-mbar increase in first-trimester atmospheric pressure (95% CI: 1.01, 1.11). This association was not altered after adjustment for temperature and humidity (odds ratio (OR) = 1.07), for first-trimester $PM_{2.5}$ level (OR = 1.06), after exclusion of the INMA Granada center (the center with the highest altitude; OR = 1.07), or after restriction to pregnancies known to involve normal delivery or unplanned cesarean delivery ($n = 45{,}135$; OR = 1.06). The association was also present after restriction to women for whom information on gestational duration based on early ultrasound measurements and information on last menstrual period were simultaneously available ($n = 27{,}058$) and reliance on either the ultrasound-based (OR = 1.06) or the last menstrual period-based definitions (OR = 1.07). It was similar after restriction to cohorts with information on changes of address during pregnancy and exclusion of women who changed addresses (OR = 1.05, 95% CI: 1.00, 1.10).

There were 429 very preterm births (0.6%). The odds ratio for very preterm delivery associated with first-trimester average atmospheric pressure was similar to that corresponding to preterm birth risk but with a wider confidence interval (OR per 5-mbar increase = 1.06, 95% CI: 0.97, 1.16). Models that adjusted for anthropometric and demographic factors also favored an increased risk of very preterm birth with higher humidity in the previous week (continuous coding of humidity, $P = 0.05$) and higher atmospheric pressure in the previous week (restricted cubic-spline coding, $P = 0.04$; Web Figure 7) but not with temperature (restricted cubic-spline coding, $P > 0.3$ for all).

Air pollution and preterm birth

The distributions of the atmospheric pollution levels are shown in Web Figures 1D–1F, and their correlations with meteorological variables are shown in Web Tables 2–3. There was no evidence of increased risk of preterm birth in association with any of the pollutants of interest averaged during all time windows considered or with traffic variables (Table 2). Estimates from full-adjustment models

Table 1. Characteristics of Live Births ($n = 71{,}493$) and Meteorological Factors Among 13 Cohorts in the European Study of Cohorts for Air Pollution Effects, 1994–2010

Characteristic	Mean (5th–95th Percentiles)	Total Population	Preterm Birth ($n = 3{,}533$)		Term Birth ($n = 67{,}960$)		χ^2 P Value
			%	Mean (5th–95th Percentiles)	%	Mean (5th–95th Percentiles)	
Maternal age, years							<0.001
<25		10,512	5.4		94.6		
25–29		23,217	4.8		95.2		
30–34		26,069	4.5		95.5		
35–39		10,122	5.5		94.5		
≥40		1,496	7.9		92.1		
Maternal education[a]							0.001
Low		13,667	5.5		94.5		
Intermediate		25,929	5.0		95.0		
High		28,742	4.6		95.4		
Mother living alone							<0.001
No		62,682	4.9		95.1		
Yes		3,250	7.5		92.5		
Parity							
0		37,701	5.6		94.4		
1		22,744	4.0		96.0		<0.001
≥2		10,448	4.8		95.2		
Sex of offspring							<0.001
Male		36,524	5.3		94.7		
Female		34,969	4.5		95.5		
Maternal smoking (second trimester), no. of cigarettes/day							<0.001
0		59,613	4.7		95.3		
1–5		5,897	5.9		94.1		
6–10		2,523	5.8		94.2		
≥10		1,240	7.2		92.8		
Maternal height, cm							<0.001
<160		9,747	6.2		93.8		
160–169		34,427	5.1		94.9		
≥170		25,956	4.2		95.8		
Maternal weight, kg[b]							<0.001
<50		2,357	7.3		92.7		
50–59		18,593	5.2		94.8		
60–69		25,000	4.5		95.5		
70–79		12,692	4.4		95.6		
≥80		9,303	5.4		94.6		
Pregnancy-related hypertension							<0.001
No		50,971	4.6		95.4		
Yes		4,549	8.2		91.8		
Cesarean delivery							<0.001
No		48,977	3.8		96.2		
Yes		8,533	11.0		89.0		

Table continues

Table 1. Continued

Characteristic	Mean (5th–95th Percentiles)	Total Population	Preterm Birth (n = 3,533)		Term Birth (n = 67,960)		χ^2 P Value
			%	Mean (5th–95th Percentiles)	%	Mean (5th–95th Percentiles)	
Season of conception							0.016
January–March		16,680	4.9		95.1		
April–June		15,928	5.4		94.6		
July–September		18,314	4.8		95.2		
October–December		20,571	4.7		95.3		
Country							<0.001
Norway		10,307	4.8		95.2		
Sweden		3,870	4.4		95.6		
Denmark		17,169	3.9		96.1		
Lithuania		4,087	5.6		94.4		
United Kingdom		9,898	5.6		94.5		
The Netherlands		19,105	5.0		95.0		
France		1,286	5.8		94.2		
Hungary		1,290	6.8		93.2		
Italy		684	5.0		95.1		
Spain		2,620	4.2		95.8		
Greece		1,177	12.7		87.3		
Temperature, °C[c]							<0.001
<5		9,812	4.3		95.7		
5–9.9		31,558	4.8		95.2		
10–14.9		25,922	5.1		94.9		
≥15		3,443	7.6		92.4		
Mean (5th–95th percentiles), °C	9.1 (3.2–14.9)			9.6 (3.4–17.4)		9.1 (3.2–14.9)	
Humidity, %[c]							<0.001
<70		8,346	6.2		93.8		
70–74.9		11,216	4.6		95.4		
75–79.9		20,000	4.4		95.6		
80–84.9		19,916	4.9		95.1		
≥85		12,015	5.4		94.6		
Mean (5th–95th percentiles), %	78 (65–89)			78 (62–89)		78 (65–89)	
Atmospheric pressure, mbar[c]							<0.001
<1,010		44,284	4.6		95.4		
1,010–1,012.9		2,126	8.6		91.4		
1,013–1,015.9		9,046	5.4		94.6		
≥1,016		11,289	5.0		95.0		
Mean (5th–95th percentiles), mbar[c]	1,004 (981–1,018)			1,004 (981–1,018)		1,004 (981–1,018)	

[a] The exact terminology for educational level varied among the studies. Low corresponds to primary schooling, intermediate to secondary schooling, and high to having at least a university degree.

[b] Before pregnancy.

[c] Average between fertilization date and the end of the 32nd week of gestation.

corresponded to a decreased risk of preterm delivery in association with nitrogen oxides (Table 2). Analyses restricted to cohorts with information allowing us to exclude planned cesarean delivery yielded similar conclusions, with point estimates associated with nitrogen oxides closer to the null association (Web Table 4). Conclusions from meta-analyses for the first-trimester exposure window were qualitatively similar to those of the pooled analyses and were in favor of between-center heterogeneity in estimates (Web Figure 8).

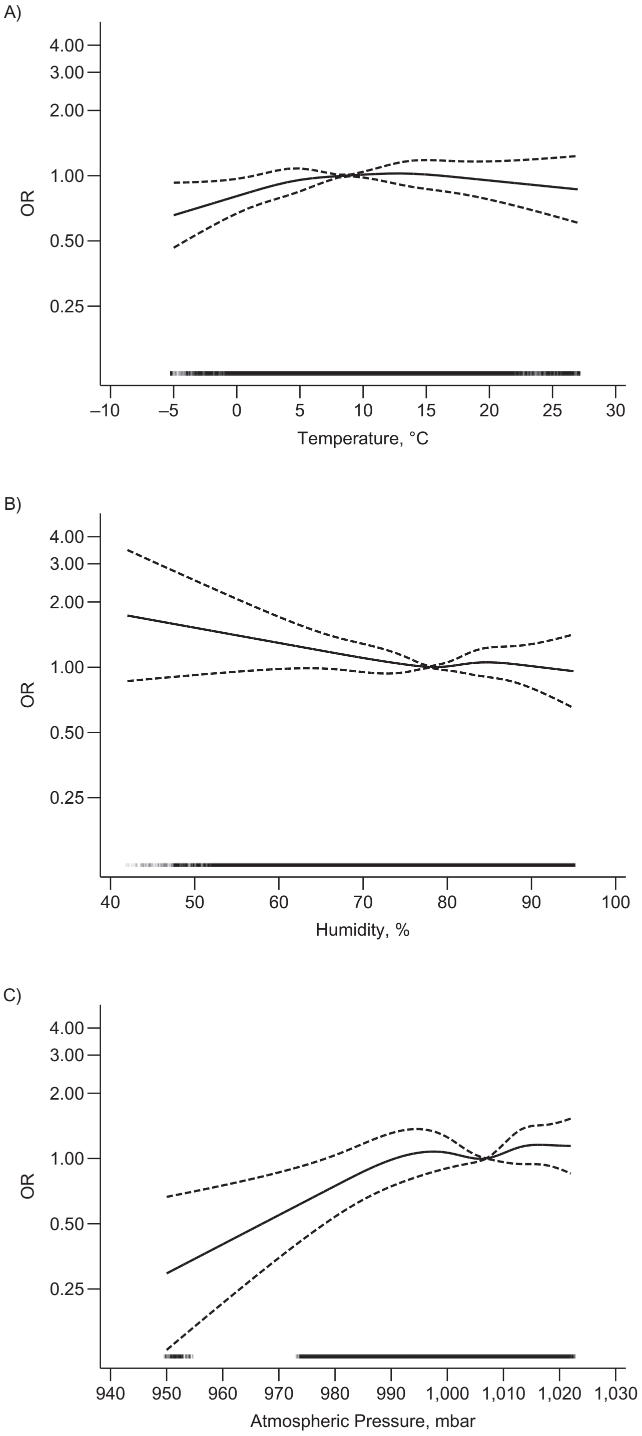

Figure 2. Adjusted odds ratios (ORs) for preterm birth associated with temperature, humidity, and atmospheric pressure, 13 cohorts in the European Study of Cohorts for Air Pollution Effects (ESCAPE), 1994–2010. A) First-trimester temperature average (63,158 births, $P = 0.08$); B) whole-pregnancy humidity average (discrete-time survival model) (63,910 births, $P = 0.41$); C) first-trimester average atmospheric pressure (59,507 births, $P = 0.03$). Restricted cubic-spline models included the adjustment factors in model 2 (see Table 2). The P value corresponds to the overall test of the spline variables in the model. For each meteorological condition, only the exposure window corresponding to the strongest statistical association was reported. For a report of associations at all exposure windows, see Web Figures 2, 5, and 6.

DISCUSSION

Our analysis of pooled data from 13 European cohorts supports an association between atmospheric pressure and preterm birth risk. There was some evidence that temperatures in the −5°C to 10°C range were positively associated with preterm birth risk and little evidence of associations with humidity and atmospheric pollutants at the levels observed in these urban areas.

The main strengths of our study include the cohort design, the harmonized and fine-scale spatial and temporal modeling of air pollution, the ability to control for a large range of potential confounders, the consideration of bias resulting from planned cesarean delivery, and the use of a survival model. Weaknesses include the fact that exposure metrics for atmospheric pollutants and meteorological factors did not incorporate the subjects' time-space activity or indoor levels. In addition, we could not distinguish preterm births in terms of associated maternal conditions (e.g., preeclampsia or infection).

The rate of preterm birth was 5% in our study, which is typical for Western European areas and much lower than in the United States, where the rate was 12% in 2010 (30). Consequently, preterm birth in the United States and preterm birth in Western Europe could be seen as distinct pathological entities, with possibly distinct risk factors, limiting comparisons between our study and US studies.

Many of the studies considering possible effects of meteorological conditions on preterm birth (6–9) focused on exposures incurred shortly before birth. These are most efficiently studied in the context of survival (or case-crossover) analyses. In a survival analysis of approximately 101,000 births in Australia, increases in 4-week temperature averages in the 15°C–25°C range were associated with an increase in preterm birth risk (6). In a case-crossover analysis in California, in which the 5th percentile of apparent temperature averaged over 6 days was 14.5°C, short-term variations in apparent temperature were associated with an increased risk of preterm birth (9). Our study focused on a lower temperature range and, if anything, highlighted possible associations with temperatures during the first-trimester time window; first-trimester temperature was not considered in the California study, due to its case-crossover design, or in the Australian study.

Living at a high altitude (entailing a lower atmospheric pressure) during pregnancy is a cause of low birth weight (31). Regarding preterm delivery, investigators in Peru reported an odds ratio for preterm birth of 1.2 (95% CI: 1.0, 1.5) for women living at an altitude of 3,000 m or more compared with women living at less than 2,000 m (32). The study in Peru did not include altitudes below 690 m, the focus in our study (32). In a report on airplane transfers of women at risk for imminent preterm delivery but not yet in labor during transfer, Akl et al. (33) observed that the airplane's reaching an altitude above 4,270 m or cabin pressure corresponding to that altitude above sea level (hence a decreased atmospheric pressure) was associated with a delayed time from landing to delivery, which, this time, is in favor of a short-term association between low atmospheric pressure and decreased preterm birth risk. Given this limited body of literature, the issue of atmospheric pressure and altitude associations with preterm birth risk warrants further investigation.

The proximal causes of preterm delivery, a highly heterogeneous condition, include inflammatory processes at the maternal-fetal interface, infections, ischemic placental dysfunction, maternal hypertension and preeclampsia, placental abruption, and preterm premature rupture of the membranes. Many of these conditions may actually be influenced by meteorology-related factors. For example, temperature, which has a clear influence on cardiac function and blood pressure outside the context of pregnancy (34, 35), may also influence the cardiovascular function of pregnant women (36, 37). Such changes in cardiac and endothelial function may in turn contribute to placental abruption, preeclampsia, or ischemic placental dysfunction. In support of this hypothesis, first-trimester temperatures have been associated with the risk of severe preeclampsia (36). The frequency of vaginal infections may vary with temperature and season (38), and some of these infections may, directly or in association with preterm premature rupture of the membranes, lead to a preterm delivery (39).

A meta-analysis of associations of air pollution with preterm birth risk showed heterogeneity in the exposure windows reported in each study (5), suggesting selective reporting of associations within studies; publication bias was also highlighted (5). This meta-analysis reported odds ratios for preterm delivery of 0.97 and 0.95 for a 20-μg/m^3 increase in first- and second-trimester PM_{10} concentrations, respectively (5), which would correspond to 0.98 and 0.97 for a 10-μg/m^3 increase in PM_{10}—very close to our adjusted hazard rate of 0.98 for both windows. The meta-analytical estimate corresponded to an increased risk of preterm birth for the whole-pregnancy (OR = 1.35) and third-trimester (OR = 1.06) exposure windows (5). It is for these exposure windows that the bias related to averaging exposures over different durations for preterm and term births is most likely to happen when logistic modeling is used—indeed, our analysis (see Web Figure 4) indicated much stronger associations with whole-pregnancy average temperature with a logistic model than with our survival-modeling approach. Such a bias is also expected for third-trimester exposures and for other seasonally varying factors, such as atmospheric pollutants. In a meta-analysis

Table 2. Associations Between Atmospheric Pollutants and Preterm Birth in a Pooled Analysis of 13 Cohorts in the European Study of Cohorts for Air Pollution Effects, 1994–2010

Pollutant and Exposure Window	Model 1[a]			Model 2[b]			Model 3[c]		
	No.	OR[d]	95% CI	No.	OR[d]	95% CI	No.	OR[d]	95% CI
NO_2									
Whole pregnancy[e]	69,503	0.97	0.93, 1.01	62,127	0.96	0.92, 1.01	56,977	0.96	0.91, 1.01
First trimester	68,042	0.96	0.93, 1.00	60,814	0.98	0.92, 1.01	55,811	0.97	0.92, 1.02
Second trimester	68,183	0.98	0.95, 1.02	60,947	0.96	0.92, 1.01	55,892	0.96	0.92, 1.01
Previous week[f]	70,210	1.01	0.98, 1.04	62,687	0.99	0.95, 1.02	57,534	0.98	0.94, 1.01
Previous month[f]	70,205	1.00	0.96, 1.03	62,684	0.97	0.93, 1.01	57,531	0.96	0.92, 1.00
NO_x									
Whole pregnancy[e]	68,215	0.98	0.93, 1.00	60,890	0.96	0.92, 1.00	55,777	0.96	0.92, 1.00
First trimester	66,762	0.96	0.93, 0.99	59,583	0.97	0.93, 1.00	54,619	0.97	0.93, 1.01
Second trimester	66,913	0.98	0.95, 1.01	59,725	0.96	0.93, 1.00	54,707	0.97	0.93, 1.00
Previous week[f]	68,932	1.00	0.98, 1.03	61,457	0.98	0.96, 1.01	56,341	0.98	0.95, 1.01
Previous month[f]	68,925	0.99	0.97, 1.02	61,452	0.97	0.93, 1.00	56,336	0.96	0.93, 1.00
$PM_{2.5}$									
Whole pregnancy[e]	56,139	0.96	0.89, 1.03	50,878	0.97	0.89, 1.05	46,791	0.96	0.87, 1.04
First trimester	55,522	0.96	0.91, 1.02	50,329	0.98	0.92, 1.05	46,242	0.98	0.91, 1.05
Second trimester	56,658	0.98	0.93, 1.04	51,316	0.98	0.92, 1.05	47,153	0.96	0.90, 1.03
Previous week[f]	57,966	1.01	0.98, 1.04	52,422	1.00	0.97, 1.03	47,776	1.00	0.96, 1.03
Previous month[f]	57,884	0.99	0.95, 1.04	52,350	0.98	0.93, 1.03	47,771	0.97	0.91, 1.02
PM_{10}									
Whole pregnancy[e]	56,139	0.95	0.87, 1.05	50,878	0.97	0.87, 1.07	46,791	0.97	0.87, 1.07
First trimester	55,522	0.97	0.90, 1.04	50,329	0.98	0.90, 1.07	46,242	0.98	0.90, 1.07
Second trimester	56,658	0.97	0.91, 1.05	51,316	0.98	0.90, 1.06	47,153	0.98	0.90, 1.06
Previous week[f]	57,966	1.00	0.96, 1.04	52,422	0.99	0.95, 1.03	47,776	0.99	0.95, 1.04
Previous month[f]	57,884	0.98	0.92, 1.03	52,350	0.97	0.91, 1.03	47,771	0.97	0.91, 1.03

Table continues

Table 2. Continued

Pollutant and Exposure Window	Model 1[a]			Model 2[b]			Model 3[c]		
	No.	OR[d]	95% CI	No.	OR[d]	95% CI	No.	OR[d]	95% CI
PM_{coarse}									
Whole pregnancy[e]	56,139	0.98	0.91, 1.06	50,878	0.99	0.91, 1.07	46,791	1.00	0.92, 1.08
First trimester	53,821	0.99	0.92, 1.06	48,874	0.99	0.91, 1.06	44,798	0.99	0.91, 1.07
Second trimester	54,985	0.99	0.92, 1.06	49,870	0.99	0.91, 1.06	45,725	1.00	0.92, 1.08
Previous week[f]	57,877	0.99	0.95, 1.03	52,346	0.99	0.95, 1.04	47,707	0.99	0.94, 1.04
Previous month[f]	57,499	0.97	0.92, 1.03	52,019	0.98	0.92, 1.05	47,747	0.98	0.92, 1.05
$PM_{2.5}$ absorbance									
Whole pregnancy[e]	57,086	0.92	0.84, 1.00	51,682	0.90	0.81, 1.00	46,846	0.92	0.82, 1.02
First trimester	55,764	0.91	0.85, 0.97	50,506	0.92	0.85, 1.00	45,713	0.95	0.87, 1.05
Second trimester	56,248	0.99	0.93, 1.06	50,967	0.97	0.89, 1.06	46,130	0.97	0.88, 1.07
Previous week[f]	58,194	1.03	0.98, 1.07	52,620	1.01	0.96, 1.07	47,781	0.99	0.94, 1.05
Previous month[f]	58,187	1.02	0.96, 1.07	52,614	0.99	0.93, 1.06	47,775	0.96	0.89, 1.04
Traffic markers									
Traffic density on nearest street	66,963	0.99	0.96, 1.02	59,676	0.99	0.96, 1.02	54,796	0.98	0.95, 1.02
Traffic load on major road within 100 m	68,391	0.97	0.94, 1.01	61,070	0.97	0.94, 1.01	55,913	0.96	0.89, 1.03

Abbreviations: CI, confidence interval; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; OR, odds ratio; PM_{10}, particulate matter with an aerodynamic diameter less than or equal to 10 µm; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 µm; PM_{coarse}, particulate matter with an aerodynamic diameter of 2.5–10 µm.

[a] In model 1, the study center was controlled for using a random-effect variable.

[b] In model 2, results were adjusted for infant sex, maternal educational level, parity (0, 1, or ≥2), season of conception, maternal smoking during second trimester of pregnancy, maternal weight (broken-stick model with a knot at 60 kg), maternal height (continuous coding), and age; study center was controlled for using a random-effect variable.

[c] In model 3, results were adjusted for all variables in model 2 and for temperature (restricted cubic-spline coding) and atmospheric pressure (continuous coding) first-trimester levels.

[d] Effect estimates are reported for a 10-µg/m^3 increase in NO_2 and PM_{10} concentrations, a 20-µg/m^3 increase in NO_x concentrations, a 5-µg/m^3 increase in $PM_{2.5}$ and PM_{coarse}, a 10^{-5}/m increase in $PM_{2.5}$ absorbance, and an increase by 5,000 vehicles per day for traffic density and by 4,000,000 vehicles per day × m for traffic load.

[e] Time-varying covariate averaged from gestational week 3 to birth or the end of gestational week 37 (whichever came first).

[f] Estimated effect of weekly or monthly air pollution levels on the risk of preterm birth the following week or month, as estimated from a discrete-time survival model censored at 37 weeks of gestation.

published in 2015 on the same topic, the whole pregnancy was the exposure window corresponding to the strongest estimated association between $PM_{2.5}$ levels and preterm birth risk (40). For the whole-pregnancy window, our findings did not favor an increased risk associated with any pollutant. For nitrogen oxides, estimates unexpectedly tended to correspond to a protective association for some exposure windows, a trend that weakened in analyses restricted to spontaneous preterm births and unplanned cesarean delivery (Web Table 4). In a large, recent study in New York, New York, Johnson et al. (41) found similar trends for protective associations. Moreover, our meta-analysis was in favor of between-city heterogeneity for associations with particulate matter. This could be explained by between-city heterogeneity in particulate-matter composition and by the heterogeneity of associations between each specific component of particulate matter and preterm birth, an issue that has been little considered (42).

Previous studies have suggested associations of atmospheric pollutants with preeclampsia risk (12) and blood pressure in pregnant women (43–45). This might imply that any effect of air pollutants on preterm birth risk is restricted to preterm births with a hypertensive etiology. However, the data available in this and in most prior studies did not allow such detailed analyses of air pollution influences on specific subtypes of preterm deliveries.

To our knowledge, few previous studies of preterm birth considered the possible confounding role of meteorological factors in the estimated effect of atmospheric pollutants (6, 9). In a case-crossover analysis of data from 16 California counties, Basu et al. (9) did not identify a significant short-term association of ozone, nitrogen dioxide, sulfur dioxide, or concentrations of fine particulate matter on preterm delivery risk independently of meteorological factors. In a birth register–based study of 101,870 births in Australia, Strand et al. (6) described the association of meteorological factors with preterm birth risk. Associations with atmospheric pollutants were not reported, and the adjustment for sulfur dioxide levels did not modify the associations between meteorological factors and occurrence of a live birth (6).

In terms of exposure assessment of atmospheric pollutants, our model included both a spatial component based on land-use regression and a temporal component based on monitoring stations (21, 26). Information on change of address was known for members of 11 cohorts, in which 15% of women moved during pregnancy, and sensitivity analyses did not support the existence of bias induced by lack of consideration of address changes. More importantly, only outdoor levels at the home address were considered. This issue also applies to temperature (and, to some extent, humidity), for which the outdoor levels assessed in meteorological networks constitute a poor proxy of the average temperature to which the woman is exposed, because people spend most of their time indoors and have different heating and window-opening habits.

In conclusion, our study highlighted an increased risk of preterm birth in association with atmospheric pressure (which could not be distinguished from altitude). Regarding temperature, preterm birth risk tended, if anything, to increase with first-trimester temperatures in the range between −5°C and 10°C. Results were not in favor of short-term (previous week or previous month) associations with temperature averages in late pregnancy, although our power to discard such associations was limited. This study did not provide additional evidence regarding an association between atmospheric pollutants at levels currently encountered in European urban areas and preterm birth risk. In future studies of associations between atmospheric pollutants and preterm birth, investigators should carefully correct for meteorological factors, which are potential confounders; rely on approaches that avoid bias due to the averaging of exposures over different durations between pregnancies with different gestational durations; and consider collecting information on maternal, fetal, and placental conditions to distinguish preterm birth cases with different proximal etiology.

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