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Maternal occupational exposures to nanoscale particles and small for gestational age outcome in the French Longitudinal Study of Children

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A R T I C L E I N F O

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A B S T R A C T

Objectives: To investigate the association between maternal occupational exposures to nanoscale particles (NPs) during pregnancy and small for gestational age (SGA).

Methods: This study included 11,224 mothers and singleton birth pairs from the French Longitudinal Study of Children (ELFE cohort), which included infants born after 33 weeks of gestation or more in continental France in 2011. Mothers who did not work during pregnancy were excluded from the analyses. Maternal occupational exposures to NPs was estimated using a job-exposure matrix for the probability (> 50%: occupationally exposed group, n = 569; 0%: occupationally non-exposed group, n = 9113; between these two thresholds: uncertain group, n = 1542) and frequency of exposure. Associations were estimated from multivariate logistic regression models for occupationally exposed *vs* occupationally unexposed groups in a first analysis, and with the frequency-weighted duration of work for the occupationally exposed group only in a second analysis.

Results: Among working mothers, 5.1% were occupationally exposed to NPs. Maternal occupational exposures to NPs was associated with SGA (ORa = 1.63, 95% CI: 1.22, 2.18). The frequency-weighted duration of work for the occupationally exposed group (n = 569) was not associated with SGA (ORa = 1.02, 95% CI: 0.97, 1.08) in adjusted analyses.

Conclusions: These results, showing a significant association between occupational exposures to NPs and SGA, should encourage further studies to examine the adverse effect of NPs exposure on fetal development.

1. Introduction

The term small for gestational age (SGA) refers to a fetus whose weight estimate falls below the 10th percentile of references available for a population (Vayssiere et al., 2015). Low birth weight (LBW) is associated with increased neonatal morbidity and mortality and morbidity in adulthood, such as cardiovascular disease, high blood pressure, type 2 diabetes, obesity, and metabolic syndrome (Chernausek, 2012; Behrman and Butler, 2007). Several factors may differentially influence birth weight. Gestational age is the major determinant of fetal growth, showing a roughly linear effect throughout the third trimester, resulting in an average 25 g per day weight increase (Mongelli and Gardosi, 1995; Wilcox et al., 1993). Many factors increase the risk of SGA, including the parents' socio-demographic characteristics (maternal age over 35 years, ethnic origin, marital status, maternal education, household income) and lifestyle (smoking, alcohol and drug use during pregnancy), the mother's health status (chronic hypertension, preeclampsia, gestational diabetes, and vascular diseases) and obstetrical history (previous SGA, multiple pregnancy, primiparity), and environmental factors (*i.e.* pesticide exposure, air pollution) (Vayssiere et al., 2015; Slama and Cordier, 2013; Gaudineau, 2013).

Several epidemiological studies have revealed a positive association between maternal exposure to ambient air pollution and adverse birth outcomes, such as LBW and SGA (Laurent et al., 2016; Dadvand et al., 2013; Pedersen et al., 2013; Stieb et al., 2012). Ambient air pollution is a complex mixture (WHO, 2006). Thus, numerous studies have attempted to identify the association between SGA and specific constituents of ambient air pollution. Of 23 studies identified in PUBMED

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concerning ambient air pollution and SGA, particulate matter (PM) exposure was considered in 15, representing most of the studies focusing on the effects of ambient air pollution on the SGA outcome. A recent meta-analysis, carried out by Zhu in 2015 found an association between exposure to PM2.5 during pregnancy and SGA (OR = 1.15; 95% CI, 1.10–1.20) (Zhu et al., 2015).PM10 and PM2.5 consist of a heterogeneous range of particle sizes. PM10 are particulate matters with aerodynamic diameter ≤ 10 μm, PM2.5 are particulate matters with aerodynamic diameter ≤ 2.5 μm (Giannini et al., 2017). Nanoscale particles (NPs) are defined as particles with at least one dimension below 100 nm. A large body of literature has reported the adverse effects of exposure to ambient air PM on human health and there is growing evidence for an important role of NPs in the observed health effects (Stone et al., 2017). Such NPs are a subset of $PM_{2.5}$ which are themselves a subset of PM_{10}. The numerical proportion of NPs is greater than that of the larger particles (PM_{10} or $PM_{2.5}$) in ambient air aerosol. In addition, at equal mass concentration, the surface area in contact with the environment is larger for aerosol NPs, conferring greater biological reactivity to such aerosols than those composed of larger particles with the same chemical composition (Ostiguy et al., 2008; Greco et al., 2015). There are three sources of NPs: naturally occurring NPs emitted from natural sources, such as volcanoes and soil erosion; so-called manufactured particles, intentionally produced by humans for commercial purposes; and the ultrafine particles unintentionally emitted by human activities (exhaust, industrial combustion) (European Union Commission, 2011; Rim et al., 2010). It has been shown that ultrafine particles and manufactured particles share the same general biological mechanisms of adverse effects, such as oxidative stress, inflammation and translocation (Stone et al., 2017; Oberdörster et al., 2005).

Recent toxicological studies have shown that exposure to NPs can disrupt development during pregnancy (Hougaard et al., 2015; Ema et al., 2016a). Developmental toxicity may potentially be induced by inhaled NPs, which may directly or indirectly interfere with the course of pregnancy and fetal development. These mechanisms are not mutually exclusive (Hougaard et al., 2015). NPs may directly affect fetal development due to their ability to cross the placental barrier, possibly reaching the fetus. In this mode of action, NPs may induce oxidative stress and inflammatory responses directly in fetal tissues. On the other hand, the indirect effects are driven by the maternal inflammatory response to NPs exposure (Hougaard et al., 2015). Based on experimental studies, the disturbance of fetal and neonatal development induced by NPs exposure is highly plausible (Blum et al., 2012; Yamashita et al., 2011; Li et al., 2009; Yoshida et al., 2010). However, there have been no epidemiological studies that have investigated the link between occupational or non-occupational prenatal maternal exposure to NPs and SGA.

Exposure is easier to assess retrospectively in a professional than extra-professional environment, using existing tools such as exposure metric matrix (Abbott and Maynard, 2010). A recent literature search that included 72 publications regarding ultrafine particles measurements showed that workers' exposure to ultrafine particles might be significantly higher than their non-occupational exposure (Viitanen et al., 2017). The aim of our study was to investigate the association between maternal occupational exposures to NPs during pregnancy and SGA.

2. Methods

2.1. ELFE study

The design of the French Longitudinal Study of Children (ELFE cohort) has been previously described by Vandentorren et al. (2009). Briefly, this cohort was launched in 2011 and enrolled children at birth and their mothers in maternity hospitals for a projected 20-year follow-up of the children. Single or twins living babies born after 33 weeks or more of gestation were included in the cohort. The acceptance rate was 51%, representing 18,040 families and 18,329 children, including 289 twins. The main objective of the ELFE study is to characterize the relationship between the environment and the development, health, and socialization of the children. The environment of the child was characterized using a multidisciplinary approach assessing socioeconomic, geographic, familial, behavior-related, physical, chemical, and microbiological exposure. A two-stage random stratified sampling design has been used. In the first stage, maternity hospitals located in continental France were randomly selected, on a national scale, from a sampling frame stratified by the status of the institution (private/public), the size and the level of medicalization (according to the number of births per year), and region (five regional clusters). Maternities that did not carry out > 365 births a year were excluded. In total, 349 maternity hospitals were randomly selected from among the total 542 in France. Among the selected maternities, 320 accepted to participate in the ELFE cohort. For the second stage of the sampling method, mothers aged 18 years and over, who gave birth to a single or two living babies after 33 weeks or more of gestation in one of the 320 maternity hospitals and who agreed to participate in the ELFE cohort, were enrolled in the study. The babies and their mothers were enrolled in four waves of four to eight days, distributed throughout the year 2011 (Vandentorren et al., 2009; Dereumeaux et al., 2016).

Data were collected through a standardized questionnaire administered face-to-face by trained interviewers (midwives, nurses, or pediatric nurses) after birth at the maternity or neonatology unit. These data pertained to the parents' socio-demographic characteristics (maternal age, marital status, maternal education, and monthly household income), job activity during pregnancy (occupation, industry sector, and time worked during pregnancy), and lifestyle (alcohol use during pregnancy and smoking status). Moreover, data pertaining to the mother's health status (weight, height, hypertension during pregnancy, gestational diabetes) and that of the child (gestational age, weight, sex, birth order, and health status) were collected through the medical files. Finally, biological samples (blood, urine, meconium, hair, and stool) were collected in the delivery room.

Two months after birth, a telephone survey was conducted to obtain new information pertaining to the development of the child and to complete any missing information from the birth questionnaire, such as work, housing, environment, and family characteristics.

2.2. Study participants

We used data from the ELFE mother-child cohort study. The present analysis was based on data collected at birth at the maternity hospital, supplemented by data from the survey carried out at the two-month follow-up. We selected mothers included in the ELFE cohort who had an occupational activity during pregnancy and gave birth to a single living infant.

2.3. Small for gestational age (SGA)

In France, the Computerized Users' Association in Pediatrics, Obstetrics, and Gynecology (AUDIPOG) carried out a modeling study of growth based on individual parameters. SGA was defined based on individual adjusted birth weight curves, taking into account the gestational age, sex, and birth order of the newborn, and the age, height, and weight of the mother (Mamelle et al., 2006; AUDIPOG, 2008).

2.4. Assessment of occupational exposure to unintentional nanoscale particles using a job-exposure matrix

Our study focused on occupational exposures to NPs. Thus, we restricted our analysis to mothers who held a job for at least one day during pregnancy. We performed a retrospective exposure assessment based on the job descriptions provided by the mothers from the beginning of pregnancy to childbirth. Occupations were coded according to the International Standard Classification of Occupations (ISCO edition 1968) (International Standard Classification of Occupations, 1968) and industry sectors were classified according to the French nomenclature of activities (NAF edition 2000) (Insee, 2000).

We characterized occupational exposures to NPs using the MatPUF job exposure matrix (JEM), which is specific for unintentionally-produced NPs. The methodology of its construction has been described previously (Audignon-Durand et al., 2016). Briefly, work processes generating unintentional nanoscale particles were identified through a comprehensive literature review and the judgement of an expert panel covering various domains, such as industrial hygiene, toxicology, physics, and atmospheric chemistry, as well as epidemiology. These work processes were linked to occupations, as defined by the ISCO edition 1968. Then, two exposure parameters were evaluated by two experts in industrial hygiene for each occupation: a probability and a frequency of exposure to NPs. The probability of exposure was defined as the proportion of individuals exposed to NPs through the implementation of work processes that generate NPs for a given occupation. It was expressed as a percentage on a semi-quantitative scale and then grouped into four categories: occupationally unexposed (0%), possible (> 0–10%), probable (> 10–50%), and very probable (> 50%) exposure. The frequency of exposure was defined as the proportion of time during which workers are exposed to NPs through the implementation of work processes that generate NPs for a given occupation (in a usually eight-hour working day). The frequency of exposure was expressed as the percentage of time spent working on a semi-quantitative scale and then grouped into four categories: sporadic (> 0–5%), occasional (> 5–30%), frequent (> 30–70%), and permanent (> 70%) exposure. The intensity of exposure was not assessed in this version, given the lack of measurement data for some work-processes and the heterogeneity of available measurement data for documented work-processes. The unexposed category implies that exposure in the considered occupation was not above the general population exposure.

We assessed maternal occupation exposures to NPs by linking the jobs held by mothers to the JEM. This allowed us to obtain an estimate of the probability and frequency of exposure to NPs for the job held during pregnancy. The JEM does not indicate whether mothers were occupationally exposed to NPs, but rather provides a probability of exposure. From the defined thresholds of probability presented in the previous paragraph, we decided to classify mothers into three groups according to occupational exposure probability to NPs obtained: occupationally non-exposed (job held during pregnancy associated with a probability of exposure of 0, n = 9113), occupationally exposed (job held during pregnancy associated with a probability of exposure > 50%, n = 569), and uncertain occupational exposure (job held during pregnancy associated with a probability of exposure > 0 but < 50%, n = 1542).

For occupationally exposed mothers (who held a job during pregnancy associated with a probability of exposure > 50%), we calculated an indicator called "the frequency-weighted duration of work", expressed in days, which corresponds to the total duration of work during pregnancy weighted by the frequency of exposure.

2.5. Statistical analysis

The odds ratios (OR) and confidence intervals (95% CI) were estimated using multivariate logistic regression models. We adjusted for potential confounders identified from the literature (Figueras and Gardosi, 2009; Lacroze, 2015; Langer, 2011; Sentilhes et al., 2017), but omitted variables already used for the construction of the SGA status. Thus, potential confounders included in the multivariate logistic regression model were monthly household income (> 4100, 2500–4100, < 2500 Euros), residential area (rural, semi-urban, urban), education (university, high school, lower than high school), marital status (alone/in a relationship with), smoking during pregnancy (yes/no), alcohol consumption during pregnancy (yes/no), pregnancy hypertension (yes/no), and gestational diabetes (yes/no).

In the main analyses, two logistic regression models were generated using non-missing data (SGA, NAF codes, ISCO codes, and working days during pregnancy and covariates): first, a model including an ever occupational exposure to NPs indicator, defining three categories (occupationally exposed, uncertain, and occupationally unexposed, with the last category being the reference category), was generated. Then, we generated a second model for the occupationally exposed group which included the frequency-weighted duration of work variable. This calculated indicator was kept as continuous quantitative variable after verification of the linearity in the logit for continuous variables, hypothesis required for logistic regressions. We used the frequency-weighted duration of work to estimate a quantitative relationship, as the matrix did not provide the intensity of exposure.

Sensitivity analyzes were also performed. First, we generated the two previously defined models adjusted for smoking, maternal education, monthly household income and high blood pressure during pregnancy (compared to the main analysis, residential area, marital status, alcohol consumption and gestational diabetes were not taken into account). Then, we re-generated the two previously defined models by modifying and varying the arbitrary threshold used to define the ever-occupationally exposed category: for the intermediate definition of exposure, occupationally unexposed group was defined by probability of exposure of 0, uncertain group by probability of exposure > 0 but < 10% and the occupationally exposed group by probability of exposure > 10%; for the sensitive definition of exposure, occupationally unexposed group was defined by probability of exposure of 0 and occupationally exposed group by probability of exposure > 0. We also performed a sensitivity analysis exclusively in children born after 37 weeks of gestation. Finally, we assumed that missing data were missing completely at random (MCAR), justifying complete data analyses. We verified the MCAR hypothesis by re-estimating the two previously defined models using a multiple imputation technique, the MICE method (multivariate imputation by chained equations) (Azur et al., 2011).

3. Results

The ELFE cohort study included 18,040 mothers. Among them, 6816 (38%) were excluded from our study: 879 mothers of twins or missing data on SGA (5%), 4363 (24%) mothers who did not work during pregnancy, and 1577 (9%) mothers missing work-related data (ISCO and NAF codes and time at work). Finally, 11,224 participants were included for analysis (Fig. 1).

Characteristics of the participants are shown in Tables 1 and 2. The mean age of the mothers was 31.0 years (standard deviation (SD): 4.7). They worked an average of 25.9 weeks during their pregnancy (SD: 7.9). The mean birth weight of their children was 3339 g (SD: 471) and the mean gestational age 39.3 weeks (SD: 1.4). Approximately 7% of the newborns were SGA. Overall, 5.1% of the participants were occupationally exposed to NPs during pregnancy. The proportion of SGA was significantly higher for the exposed group than the other groups. Maternal education, monthly household income, marital status, smoking status, body mass index, and alcohol consumption during pregnancy were significantly different between exposure groups.

Occupations held during pregnancy by the participants are described in Supplementary Tables 2 and 3. None of the mothers working in the first ten occupations most often held by the participants (47%) were classified as exposed (Supplementary Table 2). These occupations were mostly administrative, commercial, and healthcare or service occupations, such as professional nurse, government executive official, salesperson, or social worker. Among occupations held by the 569 mothers classified as exposed (Table 3), the most frequent (occupied by 75% of exposed mothers) were "cook" (19.5%), "commercial traveler

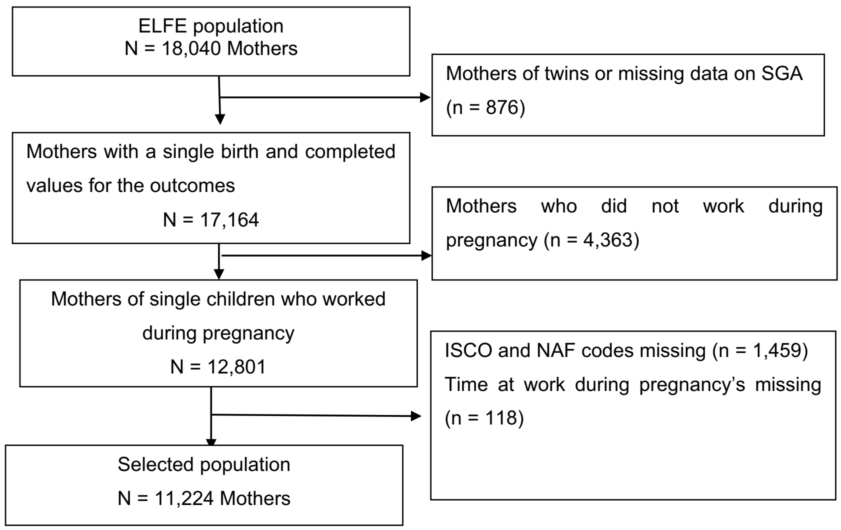

Fig. 1. Flow chart for the selection of the final population analyzed in the study on occupational exposures to nanoscale particles and SGA, ELFE Cohort, Metropolitan France, 2017.

and sales representative" (19.3%), "technical representative and service adviser" (7.0%), "motor vehicle driver" (6.9%), "working proprietor (catering and lodging service)" (5.5%), "specialized farmer" (4.6%), "street vendor" (4.0%), "baker or pastrycook" (3.5%), "confectionery maker, canvasser, newsvendor, or foreman" (2.6%), and "engineering technician" (2.3%).

For both univariate (Table 4) and multivariate analysis (Table 5), mothers who had been occupationally exposed to NPs during pregnancy had a higher risk of SGA relative to non-exposed mothers (crude odds ratio (ORc) = 1.59; 95% CI (1.20, 2.09); adjusted odds ratio (OR_{adj}) = 1.63; 95% CI (1.22, 2.18)). Among the occupationally exposed mothers (n = 569), the frequency-weighted duration of work during pregnancy was not significantly associated with SGA by univariate or multivariate analyses (ORc = 1.03; 95% CI (0.98, 1.08), OR_{adj} = 1.02; 95% CI (0.97, 1.08)).

The results of all sensitivity analyses were highly similar. The risk of SGA increased with increasing specificity of the exposed definition for the ever-exposed category, based on the occupational exposure threshold: ORadj = 1.34 (1.11, 1.61) for the most sensitive definition *vs* ORadj = 1.50 (1.22, 1.85) for the intermediate analysis and ORadj = 1.63 (1.22, 2.18) for the most specific definition (main analysis) (Table 5). While this OR was 1.49 (1.12, 1.98) in the multiple imputation analysis (Supplementary Table 5). In the sensitivity analysis concerning exclusively children born after 37 weeks of gestation, the results did not change.

4. Discussion

This study suggests that maternal occupational exposures to NPs during pregnancy are associated with a higher risk of SGA in the offspring. The sensitivity analyses showed a gradient for the association: the higher the threshold used to define the exposed group, the higher the odds ratio. This supports the consistency of our results. However, there was no clear trend for the frequency-weighted duration of work among exposed mothers.

One strength of our study was the analysis of data from a large cohort (ELFE), with many collected variables, and the ability to code most of the mothers' occupations.

This is the first observational study to examine the association between occupational exposures to NPs and SGA. However, several studies have investigated the association between SGA and exposure to PM_{10} or $PM_{2.5}$ from outdoor air pollution. In a recent meta-analysis conducted by Zhu et al. (2015), a comprehensive quantitative analysis of the results showed that $PM_{2.5}$ can increase the risk of low birth weight (OR = 1.05; 95% CI, 1.02–1.07), preterm birth (OR = 1.10; 95% CI, 1.03–1.18), and SGA (OR = 1.15; 95% CI, 1.10–1.20). A recent study conducted with the placentas of 668 newborns demonstrated that air pollutants (PM_{10} and nitrogen dioxide) exposures during pregnancy are associated with placental gene methylation and provides some mechanistic insight into some of the reported effects of air pollutants (Abraham et al., 2018). These results are consistent with our findings concerning occupational exposures to NPs.

These results are biologically plausible, as several toxicological studies in animals have demonstrated pathophysiological mechanisms

Table 1
Characteristics of participants depending on exposure status. Quantitative variables. N = 11,224, ELFE sub-study on occupational exposures to nanoscale particles (NPs), Metropolitan France, 2017.

	Total (n = 11,224)			Unexposed (n = 9113)			Uncertain (n = 1542)			Exposed (n = 569)			p-Value[a]
	Means	± SE	Min - max	Means	± SE	Min - max	Means	± SE	Min - max	Means	± SE	Min – max	
Maternal age (years)	31.0	± 4.7	18.1–48.7	31.2	± 4.5	18.4–48.7	30.5	± 5.2	18.3–45.9	30.4	± 4.9	20.1–47.2	< 0.0001
Time worked during pregnancy (weeks)	25.9	± 7.9	0.1–41.9	26.1	± 7.5	0.1–41.3	24.6	± 8.8	0.3–41.9	24.8	± 9.2	0.1–41.3	< 0.0001
Child birth weight (gram)	3339	± 471	1320–5540	3339	± 466	1335–5540	3337	± 492	1320–5475	3322	± 478	1870–4800	0.6897
Gestational age (weeks of gestation)	39.3	± 1.4	33.0–42.0	39.3	± 1.4	33.0–42.0	39.2	± 1.4	33.0–42.0	39.4	± 1.4	33.0–42.0	0.1165

SE: standard error; min: minimum; max: maximum; n: number of participants; unexposed: probability of exposure = 0; uncertain: probability of exposure between 0 and 50%; exposed: probability of exposure > 50%.

[a] Kruskall-Wallis test to compare quantitative variables.

Table 2
Characteristics of the participants depending on exposure status. Qualitative variables. N = 11,224, ELFE sub-study on occupational exposures to nanoscale particles, Metropolitan France, 2018.

	Total (n = 11,224)		Occupationally unexposed (n = 9113)		Uncertain (n = 1542)		Occupationally exposed (n = 569)		p-Value[a]
	n	%	n	%	n	%	n	%	
Small for gestational age									0.0004
Yes	825	7.4	630	6.9	135	8.8	60	10.5	
No	10,399	92.7	8483	93.1	1407	91.3	509	89.5	
Maternal education									< 0.0001
University	7780	69.3	6831	75.0	634	41.1	315	55.4	
High school	2081	18.5	1519	16.7	421	27.3	141	24.8	
Lower	1363	12.1	763	8.4	487	31.6	113	19.9	
Monthly household income (euros)[b]									< 0.0001
> 4100	2644	24.7	2237	25.7	306	20.9	101	18.7	
2500 to 4100	6000	56.0	5101	58.6	630	43.0	269	49.9	
1 to 2500	2064	19.3	1365	15.7	530	36.2	169	31.4	
Marital status[b]									< 0.0001
In a relationship	10,705	95.5	8750	96.1	1418	92.1	537	94.5	
Single	504	4.5	352	3.9	121	7.9	31	5.2	
Residential area									0.0633
Rural	314	2.8	247	2.7	41	2.7	26	4.6	
Semi-urban	3757	33.5	3062	33.6	498	32.3	197	34.6	
Urban	7153	63.7	5804	63.7	1003	65.1	346	60.8	
Smoking during pregnancy[b]									< 0.0001
No	8430	75.5	7011	77.4	1035	67.5	384	67.6	
Yes (active or passive)	2735	24.5	2052	22.6	499	32.5	184	32.4	
Alcohol during pregnancy[b]									0.0114
No	8293	74.2	6736	74.3	1163	75.9	394	69.5	
Yes	2877	25.8	2335	25.7	369	24.1	173	30.5	
High blood pressure[b]									0.3407
No	10,675	96.7	8665	96.7	1464	96.4	546	97.7	
Yes	366	3.3	298	3.3	55	3.6	13	2.3	
BMI before pregnancy									< 0.0001
Thin (BM I < 18.5)	824	7.3	664	7.29	115	7.5	45	7.9	
Normal (BMI = [18.5–25.0])	7555	67.3	6237	68.4	941	61.0	377	66.3	
Overweight (BMI = [25.0–30.0])	1912	17.0	1512	16.6	300	19.5	100	17.6	
Obese (BMI ≥ 30.0)	933	8.3	700	7.7	186	12.1	47	8.3	
Gestational diabetes[b]									0.9951
No	10,243	92.9	8318	92.9	1410	92.8	515	92.8	
Yes	784	7.1	638	7.1	109	7.2	40	7.2	
Child's sex									0.4550
Male	5773	51.4	4685	51.4	782	50.7	306	53.8	
Female	5451	48.6	4428	48.6	760	49.3	263	46.2	

Missing data on monthly household income (n = 516), marital status (n = 15), smoking status during pregnancy (n = 59), alcohol during pregnancy (n = 54), high blood pressure (n = 183), and on gestational diabetes (n = 197).

[a] Chi-square or Fisher test.

[b] Analysis of available data.

that may influence birth weight after exposure to nanoscale particles (Hougaard et al., 2015; Yamashita et al., 2011; Ema et al., 2016b; Valentino et al., 2016; Srinivas et al., 2011). Nanoscale particles have been shown in animal studies to be able to cross the alveolar-capillary barrier, due to their small size and high diffusion capacity, and then diffuse into the bloodstream, accumulate in the placenta, and cross the placental barrier to directly interfere with the development of the fetus (Hougaard et al., 2015; Ema et al., 2016b). Inhalation of nanoscale particles was shown in a rabbit model by Valentino et al. (2016) to decrease placental vascularization and perfusion, reducing maternal-fetal exchange. Histopathological and functional abnormalities of the placenta induced by exposure to nanoscale particles leads to intrauterine growth retardation. Yamashita et al. (2011) showed that nanoscale particles accumulating in the placenta of pregnant mice induce thrombi formation, causing placental dysfunction and abnormal fetal growth, particularly intrauterine growth retardation. In the study of Valentino et al. (2016), nanoscale particles were found in the placental trophoblastic cell cytoplasm, particularly in endosomes and lysosomes, suggesting nanoscale particles may be transported into placental cells through endocytosis. Nanoscale particles may also indirectly interfere with the development of the fetus through a systemic inflammatory response. This biological response may slow or even halt fetal development in animal-based models through the production of cytokines, which may reach the fetus and interfere with normal development (Hougaard et al., 2015; Srinivas et al., 2011).

We performed a standardized and automatic exposure assessment using the MATPUF JEM. This provided a frequency and probability of exposure for the occupations held by mothers during pregnancy. However, no information regarding the intensity of exposure was available. We estimated the dose-response relationship using an imperfect indicator, namely the frequency-weighted duration of work among exposed mothers. Although we found a positive association with the ever-occupationally exposed status, no significant association was observed with this quantitative exposure indicator. A possible explanation among others could be that mothers who were occupationally exposed to nanoscale particles over a long period of time could be exposed at lower intensities, whereas mothers occupationally exposed at higher intensities could be exposed for a shorter duration. In addition, we could not take into account the timing of exposure, which might be an important parameter to consider when pregnancy outcomes are investigated. Indeed, it has been shown for other pollutants that a given exposure may have a different effect on fetal development depending on when it occurred during pregnancy (Birks et al., 2016).

The use of a JEM did not allow us to consider inter-individual

Table 3
The exposing jobs (Jobs with probability of exposure to nanoscale particles > 50%), among exposed mothers (N = 569).

Exposing jobs	Frequency	Percent
Cook	111	19.51
Commercial traveler and manufacturers' agent	110	19.33
Technical salesman and service adviser	40	7.03
Motor vehicle driver	39	6.85
Working proprietor (catering and lodging service)	31	5.45
Specialized farmer	26	4.57
Street vendor, canvasser and newsvendor	23	4.04
Baker, pastrycook and confectionery maker	20	3.51
Foreman	15	2.64
Engineering technician n.e.c.	13	2.28
Orchard, vineyard and related tree and shrub crop worker	13	2.28
Nursery worker and gardener	11	1.93
Painter, construction	11	1.93
Livestock worker	10	1.76
Mechanical engineer	9	1.58
Agronomist and related scientist	8	1.41
Field crop and vegetable farm worker	8	1.41
Chemist	7	1.23
Civil engineering technician	6	1.05
General farm worker	5	0.88
General farmer	5	0.88
Manager (catering and lodging services)	5	0.88
Chemical engineering technician	4	0.70
Mechanical engineering technician	4	0.70
Agricultural and animal husbandry worker n.e.c.	3	0.53
Fire-fighters	3	0.53
Jewelry and precious metal worker	3	0.53
Bricklayer, stonemason and tile setter	2	0.35
Chemical engineer	2	0.35
Dairy farm worker	2	0.35
Farm manager and supervisor	2	0.35
Musical instrument maker and tuner	2	0.35
Physical science technician	2	0.35
Poultry farm worker	2	0.35
Sheet-metal worker	2	0.35
Aircraft pilot, navigator and flight engineer	1	0.18
Carpenter, joiner and parquetry worker	1	0.18
Civil engineer	1	0.18
Electrical and electronic equipment assembler	1	0.18
Electrical fitter	1	0.18
Forestry worker (except logging)	1	0.18
Glass former, cutter, grinder and finisher	1	0.18
Life science technician	1	0.18
Machinery fitter and machine assembler	1	0.18
Metallurgist	1	0.18

variability within homogeneous exposure groups defined by occupations (row of the JEM). Such a limitation could have led to misclassifications, which were likely to be non-differential, thus leading to an under-estimation of the association under investigation (Burstyn et al., 2014). In addition, the JEM did not provide an estimate of indirect exposure due to the work environment. We estimated the association between SGA and occupational exposures to NPs in a binary manner (occupationally exposed *vs* not occupationally exposed). Thus, we may have classified some mothers as not occupationally exposed while they were actually occupationally exposed through indirect exposure, thus leading to a dilution of the estimated effect.

We had to specify a threshold above which mothers were defined as occupationally exposed because the JEM only provides a probability of exposure. We adopted a specific definition of the occupationally exposed group *a priori* by defining a threshold above which mothers were considered to be occupationally exposed (probability of exposure > 50%). We also considered mothers below this threshold to have an uncertain status to obtain a true occupationally unexposed group. Such choices may have influenced our conclusions. Thus, we performed sensitivity analyses by considering various thresholds, but the conclusion remained the same: we observed a significant association between occupational exposures to NPs and SGA irrespective of the analysis

Table 4
Association between maternal occupational exposures to nanoscale particles (NPs), mothers' characteristics, and SGA. Univariate logistic regression. N = 11,224 mothers, sub-study ELFE, Metropolitan France, 2018.

	N	OR	95% CI	p[*]
Occupation exposures to NPs	11,224			0.0005
Unexposed (0)	9113	Ref		
Uncertain (> 0–0.5)	1542	1.29	(1.06, 1.57)	
Exposed (> 0.5)	569	1.59	(1.20, 2.09)	
Education	11,224			0.0002
University	7780	Ref		
High school	2081	1.35	(1.13, 1.61)	
Lower	1363	1.39	(1.13, 1.70)	
Monthly household income[a]	10,708			0.0045
> 4100 Eur	2644	Ref		
2500 to 4100 Eur	6000	1.28	(1.06, 1.54)	
1 to 2500 Eur	2064	1.44	(1.15, 1.79)	
Residential area	11,224			0.5931
Rural	314	Ref		
Semi-urban	3757	0.84	(0.55, 1.30)	
Urban	7153	0.90	(0.59, 1.34)	
Marital status[a]	11,209			0.0843
In a relationship	10,705	Ref		
Single	504	1.31	(0.96, 1.79)	
Smoking during pregnancy[a]	11,165			< 0.0001
No	8430	Ref		
Yes (active or passive)	2735	1.80	(1.55, 2.09)	
High blood pressure[a]	11,041			< 0.0001
No	10,675	Ref		
Yes	366	2.92	(2.22, 3.86)	
Gestational diabetes[a]	11,030			0.7829
No	10,243	Ref		
Yes	787	1,04	(0.79,1.37)	
Alcohol during pregnancy[a]	11,170			0.7132
No	8293	Ref		
Yes	2877	0.97	(0.82, 1.14)	

OR: crude odds ratio, CI: confidence interval, N: number.
[*] p-Value: Chi-2 of Wald test.
[a] Variable with missing data.

performed. As expected, the more sensitive the definition, the more the estimated effect was weaker, showing our results to be consistent.

We only considered occupational exposure. However, mothers could have been exposed to NPs in non-occupational settings, *i.e.* from indoor or outdoor air pollution. This would lead to a confounding bias in our results only if the distribution of such non-occupational exposure was different between the exposed and non-exposed groups. If the distribution of non-occupational exposures was equivalent and of the same magnitude among the occupationally exposed and occupationally unexposed mothers, it should have had no effect on our estimations. However, if mothers defined as occupationally unexposed in our analysis were indeed exposed to nanoscale particles in non-occupational settings, this may have led to an underestimation, which seems unlikely.

We tried to carefully adjust for potential confounding factors (smoking, marital status, maternal education, monthly household income, high blood pressure during pregnancy, gestational diabetes, and alcohol consumption during pregnancy). However, we considered smoking status only as a categorical variable and did not consider the number of cigarettes smoked during pregnancy. Smoking may represent an important confounding factor because it is highly associated with SGA and may be associated with occupational exposure to nanoscale particles due to socio-economic status. Unfortunately, quantitative data for tobacco smoking during pregnancy were not available and we only had information concerning the tobacco smoking status, *i.e.* ever smoker during pregnancy *vs* never smoker during pregnancy, potentially leading to residual confounding. In addition, we did not consider other occupational exposures which could be associated with both SGA and NPs, making them confounding factors (Ahmed and Jaakkola, 2007; Chen et al., 2006; Casas et al., 2015). Among the occupations

Table 5
Association between maternal occupational exposures to nanoscale particles (NPs) and SGA. Multivariate logistic regression (main analysis). N = 10,305 mothers, sub-study ELFE, Metropolitan France, 2018.

	Main analysis					Intermediate analysis					Sensitive analysis				
		N	ORadj	95% CI	p*		N	ORadj	95% CI	p*		N	ORadj	95% CI	p*
Occupation exposures to NPs					0.0016					0.0007					0.0019
Unexposed	0%	8369	Ref			0%	8369	Ref			0%	8369	Ref		
Uncertain	> 0–50%	1418	1.23	(0.99, 1.52)		> 0–10%	748	1.06	(0.79, 1.42)						
Exposed	> 50%	518	1.63	(1.22, 2.18)		> 10%	1188	1.50	(1.22, 1.85)		> 0%	1936	1.34	(1.11, 1.61)	
Frequency-weighted duration of work (/days)															
Exposed	> 50%	518	1.02	(0.97–1.08)		> 10%	1188	1.03	(0.99–1.07)		> 0%	1936	1.04	(1.01–1.08)	

Adjusted for smoking, marital status, residential areas, maternal education, monthly household income, high blood pressure during pregnancy, gestational diabetes and alcohol consumption during pregnancy; p* p-value (Chi2 of Wald test); ORadj: adjusted odds ratio; CI: confidence interval; N: number.
In bold: statistically significant associations.

with probabilities of exposure > 50% (classified as occupationally exposed), we did not observe any common factors between these occupations that could be linked to occupational exposure and skew our results. A multidisciplinary team (occupational physician, industrial hygienist, and epidemiologists) reviewed all exposure-related job titles and assessed them for other occupational exposures to rule them out as additional confounding factors.

One of the limitations of our work is the lack of consideration of ambient air pollution. These data were not available from data collected in the Elfe study. As suggested in a recent study conducted in France, highlighted social inequalities in atmospheric pollutants exposure (Ouidir et al., 2017), we introduced in the final model in addition to other relevant confounders, variables in relation to socio-economic status such as household income, education and marital status. The "residential area" variable was also included in the final model.

We excluded women who did not work during pregnancy from our study sample. Some studies have shown that working populations, particularly women, are healthier than non-working populations (47). Thus it is possible that the "healthy worker" effect might be a source of differences in pregnancy outcomes, particularly the birth weight of newborns (Casas et al., 2015; Shah, 2009). In the context of this study, we opted for an analysis restricted to women who worked during pregnancy, knowing that this choice would limit the generalization of the results to women who worked during pregnancy.

We excluded subjects from our study sample due to missing data for the main variables of interest (adjustment variables and SGA) and performed analyses on complete data. We analyzed the whole dataset using multiple imputation by the chained equations method to verify that these data were missing completely at random (Supplementary Table 5). The results were quite similar to those of our main analysis, showing that subject selection based on the completeness of the data should not have influenced our results.

5. Conclusion

This is the first epidemiological study to show a significant association between maternal occupational exposures to NPs during pregnancy and SGA. These results are consistent with the epidemiological literature based on air pollution, as well as the toxicological literature. Transplacental transfer of NPs and their fetotoxicity has been established in several animal models. These first results should encourage the development of further studies to examine the adverse effects of NPs exposure on fetal development. Moreover, further studies aiming to precisely determine the doses and entry routes for occupational or non-occupational exposure should be performed.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.11.027.

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