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**Maternal occupational exposure to carbonaceous nanoscale particles and small for gestational age and the evolution of head circumference in the French Longitudinal Study of Children - Elfe study**

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## **ABSTRACT**

**Objectives:** To investigate the association between exposure to unintentionally emitted carbonaceous nanoscale particles (NPs) and small for gestational age (SGA), as well as head circumference (HC) at birth and at two years of age.

**Methods:** Mothers from the French Longitudinal Study of Children (Elfe cohort) who worked during pregnancy were selected for our study. Data collected at birth and during follow-up (up to two years) were used. The probability and frequency of maternal occupational exposure to unintentionally emitted carbonaceous NPs was estimated using a job exposure matrix (MatPUF). Multivariate logistic regression, linear regression, and mixed models were applied to estimate any associations. Analyses were carried out depending on whether mothers stopped working during the first, second, or third trimester of pregnancy.

**Results:** Maternal occupational exposure to unintentionally emitted carbonaceous NPs was associated with SGA in the overall study population by multivariate analysis (OR<sub>a</sub>=1.80, 95% CI: 1.29, 2.46), as well as in sub-groups of mothers who stopped working during the second (OR<sub>a</sub>=1.84, 95% CI: 1.13, 3.02) or third (OR<sub>a</sub>=1.80, 95% CI: 1.10, 2.95) trimesters. There were no significant associations with HC at birth or two years of age.

**Conclusions:** We found a significant association between occupational exposure to carbonaceous NPs and SGA, with the effect depending on the period of exposure during pregnancy. These results should encourage further studies concerning the adverse effects of exposure to carbonaceous NPs on the development of offspring.

**Keywords:** Small for gestational age; head circumference; occupational exposure; carbonaceous nanoscale particles; Elfe cohort.

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## 1. Introduction

Intrauterine life is highly susceptible to a variety of toxicants, including atmospheric pollutants (Li et al. 2019). Atmospheric particulate matter (PM) with an aerodynamic diameter of  $\leq 10 \mu\text{m}$  ( $\text{PM}_{10}$ ) or  $\leq 2.5 \mu\text{m}$  ( $\text{PM}_{2.5}$ ) has been shown to potentially induce reduced birth weight (Dadvand et al. 2013; Li et al. 2019; Zhu et al. 2015) and occipitofrontal circumference at birth (Clemens et al. 2017; Jedrychowski et al. 2004; Lamichhane et al. 2018; van den Hooven et al. 2012). Low birth weight has been associated with high rates of neonatal morbidity and mortality and long-term adverse health effects, such as cardiovascular diseases, metabolic syndrome, high blood pressure, obesity, and type 2 diabetes mellitus (Chernausk 2012; Salam et al. 2014). Head circumference (HC) at birth reflects the brain volume and is used as an indicator of *in utero* brain development (Barbier et al. 2013). Slow head growth during pregnancy has been correlated with impaired neuropsychological development later in life (Gale et al. 2006; Veena et al. 2010). Among the observed effects of exposure to PM from ambient air pollution (*e.g.* reduced birth weight and HC), nanoscale particles (NPs) have recently been ascribed to play an important role (Stone et al. 2017). NPs are particles with at least one dimension  $< 100 \text{ nm}$  (EU 2011). They are generally called nanoparticles when intentionally manufactured by humans and ultrafine particles (UFP) or unintentional nanoscale particles (UNPs) when produced unintentionally (Oberdorster et al. 2005). During certain work processes, particles of various chemical families can be unintentionally emitted (Audignon-Durand et al. 2016; Borm et al. 2006; Chen et al. 2017): carbonaceous particles (polycyclic aromatic hydrocarbon particles and particles of carbon) from the thermal degradation of organic matter and mechanical degradation of carbon, metal and metal oxide particles from the mechanical and thermal degradation of metals, and mineral particles from the mechanical and thermal degradation of minerals.

Unintentional and manufactured particle toxicology are not two distinct fields, but overlap extensively. Thus, biopersistent NPs share the same general biological mechanisms of adverse effects (Oberdorster et al. 2005; Stone et al. 2017). Based on animal models, maternal exposure to nanoparticles during pregnancy may alter the *in* and *post utero* development of offspring (Blum et al. 2012; Yamashita et al. 2011). The mechanisms described for the alteration of birth weight are essentially placental

(Hougaard et al. 2015). Toxicological studies have shown that adverse effects may occur due to translocation of nanoparticles from the respiratory tract to the placenta, reducing maternal fetal exchange and causing oxidative stress that can induce or aggravate local inflammation or directly alter fetal tissue after crossing the placental barrier. Fetal adverse effects may also indirectly occur through maternal inflammatory responses (Ema et al. 2016; Hougaard et al. 2015). Furthermore, NPs can cross the blood-brain barrier (Bakand and Hayes 2016; Zhang et al. 2018) and lead to an increase in oxidative stress and/or a decrease in the number of neurotransmitters in the cerebral cortex, causing central nervous system disorders (Zhang et al. 2018).

We recently published an initial study that showed a significant association between occupational exposure to UNPs and small for gestational age (Manangama et al. 2019). However, this study did not specify the chemical type of NPs involved in the observed effect. Only a few epidemiological studies have examined the association between PM composition and birth weight. The PM components most frequently associated with low birth weight cited by published studies are carbonaceous particles (Basu et al. 2014; Bell et al. 2010; Ebisu and Bell 2012; Laurent et al. 2014; Laurent et al. 2016; Wilhelm et al. 2012). Carbonaceous particles constitute a substantial proportion of airborne particulate matter (PM) for both the general population (Heal 2014; Putaud et al. 2004; Putaud et al. 2010) and in the work place (Leoni et al. 2016; Morawska and Zhang 2002). Furthermore, a recently published study reported, for the first time, the presence of carbonaceous particles in the placentas of women exposed during pregnancy in real-life conditions (Bové et al. 2019). Similarly, a recent review reported that black carbon particles translocate from the respiratory tract to the human placenta at both the maternal and fetal side, causing placental modifications (Saenen et al. 2019). These data confirm that particles can be translocated directly towards the fetus and potentially explain the adverse effects.

The main objective of this study was to investigate the association between maternal occupational exposure to unintentionally emitted carbonaceous NPs during pregnancy and the child's *in* and *post-utero* development. The two specific objectives were to investigate the association between exposure to unintentionally emitted carbonaceous NPs and SGA and the association between exposure to unintentionally emitted carbonaceous NPs and HC at birth and two years of age.

## 2. Methods

### 2.1. Elfe study

The design of the French Longitudinal Study of Children (Elfe cohort) was described in 2019 in a dedicated article (Charles et al. 2019). Briefly, the Elfe cohort is a survey, launched in 2011, that enrolled children born at 33 weeks or more of gestation in maternity hospitals in mainland France for a projected 20-year follow-up. It is a mother-child cohort that aims to characterize the relationship between the environment and the child's health, development, and socialization. The inclusion of participants took place in four waves of four to eight days, spread out over the year to account for possible seasonal variations. The study was offered to all mothers giving birth in 320 maternity units that agreed to participate among the 349 randomly selected in metropolitan France. In total, 18,040 families and 18,329 children were selected. Among the 18,040 families who gave their consent at birth, follow-up surveys were conducted for 16,281 families (90.2%) at two months, 14,439 families (80.0%) at one year, and 13,277 families (78%) at two years. Several types of data were collected, including data on socio-demographic characteristics, lifestyle, health data, environmental exposure data, and data on maternal occupation and occupational exposure. At the maternity ward, data were collected via a face-to-face questionnaire administered by a trained midwife or nurse. These data were supplemented with data from the birth medical record and biological samples taken in the delivery room. During the follow-up, data were collected through telephone surveys and from the children's primary-care physician.

### 2.2. Study participants

We selected consenting mothers who gave birth to a single living infant and worked at least one day during pregnancy.

### 2.3. Small for gestational age

This binary variable (yes/no) was defined according to individual adjusted birth-weight curves, taking into account the sex, birth order, and gestational age of the newborn and maternal parameters (age,

height, and weight) (AUDIPOG 2008; Mamelle et al. 2006). SGA data were collected in the child's medical file at the maternity ward.

#### 2.4. Head circumference

HC corresponds to the occipitofrontal circumference measurements of the child expressed in cm. It was one of the anthropometric parameters measured at birth and during the various follow-ups of the Elfe cohort. HC data were collected from the child's medical file at the maternity ward for the HC at birth and from the child's health record booklet for the HCs during follow-up. The HC values during follow-up were recorded by the child's primary care physician.

#### 2.5. Assessment of occupational exposure to unintentional NPs using a job-exposure matrix

Occupational exposure to NPs was characterized using a specific job exposure matrix (JEM) for unintentionally-produced NPs, MatPUF. The methodology used for its construction and practical application has been described previously (Audignon-Durand et al. 2016; Manangama et al. 2019). Briefly, the work processes that generate UNPs were identified on the basis of monitoring and bibliographic analyses and the opinion of a multidisciplinary group of experts. In total, 57 work processes were identified and validated as likely to emit UNPs during their implementation. For each work process, the chemical families of potentially emitted UNPs were then characterized. This analysis identified six chemical families as follows: 1) metals and metal oxides from the mechanical and thermal degradation of metals, 2) minerals from the mechanical and thermal degradation of (non-metallic) minerals, 3) carbonaceous particles (elemental carbon or polycyclic aromatic hydrocarbon) from the mechanical degradation of carbon and thermal degradation of organic matter, 4) wood, cellulose, and plant particles from the mechanical degradation of wood, cellulose, and plants, 5) polymers from the mechanical and thermal degradation of polymers, mainly plastics, and 6) other organic particles (organic food or non-food organic products of animal origin) resulting from the mechanical degradation of organic food or non-food organic products of animal origin. Our study focused on carbonaceous particles. Two parameters were evaluated for each process: the probability and frequency of exposure. The probability of exposure was defined as the proportion of individuals

exposed through the implementation of work processes that generate NPs for a given occupation. The frequency of exposure was defined as the proportion of time, daily, during which workers were exposed through the implementation of work processes that generate NPs for a given occupation (in a typical eight-hour working day).

Jobs were characterized by occupations coded according to the International Standard Classification of Occupations (ISCO edition 1968) and industry sectors coded according to the French nomenclature of activities (NAF2000). Maternal occupational exposure was assessed by linking the jobs held by mothers during pregnancies to the JEM. The JEM estimates a probability and frequency of exposure for each occupation and industry sector. We then obtained an estimate for each selected mother of the probability and frequency of occupational exposure during pregnancy for each chemical family assessed in the MatuPUF JEM, specifically carbonaceous particles. According to the probability of occupational exposure to carbonaceous NPs (exposure to elemental carbon and/or polycyclic aromatic hydrocarbon) obtained after using the MatPUF, we classified mothers into three groups: occupationally unexposed (job held during pregnancy associated with a probability of exposure of 0), occupationally exposed (job held during pregnancy associated with a probability of exposure > 50%), and uncertain occupational exposure (job held during pregnancy associated with a probability of exposure > 0 but < 50%). A computed indicator called « the frequency-weighted duration of work », expressed in weeks, was then used only for mothers who were occupationally exposed to carbonaceous NPs (who held a job during pregnancy associated with a probability of exposure > 50%). This indicator corresponds to the total duration of work during pregnancy weighted by the frequency of exposure.

## 2.6. Statistical analysis

We examined the association between maternal occupational exposure to unintentionally emitted carbonaceous NPs during pregnancy and SGA using multivariate logistic regression models. These analyses were carried out on the overall study population and then depending on whether the mothers stopped working during the first, second, or third trimester of pregnancy. All measures of association were reported with their 95% confidence intervals (CI) adjusted for potential cofounders identified

from the literature, but omitted variables already used for the construction of the SGA status. Thus, analyses were adjusted for smoking during pregnancy (yes/no), marital status (living alone/with the spouse), residential area (rural, semi-urban, urban), maternal education (university, high school, lower than high school), monthly household income (> 4,100, 2,500-4,100, < 2,500 euros), high blood pressure during pregnancy (yes/no), gestational diabetes (yes/no), and alcohol consumption during pregnancy (yes/no).

We examined the association between maternal occupational exposure to unintentionally emitted carbonaceous NPs during pregnancy and HC at birth using multivariate linear regression models. The basic hypotheses of the linear models were verified by the residuals analysis method. These analyses were carried out on the overall study population and then depending on whether the mothers stopped working during the first, second, or third trimester of pregnancy. All measures of association were reported with their 95% confidence intervals (CI) adjusted for potential cofounders identified from the literature. Thus, analyses were adjusted for maternal education (university, high school, lower than high school), smoking status during pregnancy (yes/no), high blood pressure during pregnancy (yes/no), gestational diabetes (yes/no), residential area (rural, semi-urban, urban), and the child's sex and gestational age.

We modelled the change in HC between birth and the two-year follow-up by applying a mixed model with an interaction with time and random effects on the intercept and slope. The age of the child at the various follow-ups was considered as time. After verifying the linearity hypothesis, the quantitative variables 'age during follow-up' and 'frequency weighted duration of work during pregnancy' were transformed into a logarithm scale. The analyses were carried out on the overall study population and then depending on whether the mothers stopped working during the first, second, or third trimester of pregnancy. Potential cofounders were identified from the literature. Thus, analyses were adjusted for parental smoking status, monthly household income (> 4,100, 2,500-4,100, < 2,500 euros), residential area, maternal education, and child' sex.

For each analysis (regressions and mixed models), two models were generated: the first model included ever-occupational exposure to NPs as the main explicative variable, defining three categories:

occupationally exposed, uncertain, and occupationally unexposed, with the last category being the reference category. The second model was only generated for the occupationally exposed group and included the « frequency-weighted duration of work » during pregnancy as the main explicative variable. As the matrix did not provide the intensity of exposure, we used the frequency-weighted duration of work to estimate a quantitative relationship between exposure and outcome.

We considered the missing data for the variables of interest (SGA, HC, and covariables) to be missing completely at random (MCAR) in the Elfe cohort. Thus, we conducted our analyses on the available data (Leffondre et al. 2015). We verified the MCAR hypothesis by re-estimating the models using the multiple imputation method, MICE (multivariate imputation by chained equations). All analyses were conducted using R-3.5.2 and SAS9.4.

### 3. Results

Among the 18,040 mothers included in the Elfe cohort, 12,073 (66%) were selected for our analyses. Certain mothers were excluded from this selected population because of missing data on the dependent variables. Analyses concerning SGA were conducted for 11,224 mothers and those concerning HC at birth for 10,734 mothers. During follow-up, HCs were recorded for 5,795 children at one month, 5,232 children at two months, 8,050 children at four months, 7,796 children at nine months, 6,991 children at 12 months, and 4,825 children at 24 months (Fig. 1).

The characteristics of the study population in terms of SGA outcome have already been described in our previous study (Manangama et al. 2019). Certain characteristics at birth of the selected population (with available data on HC) according to occupational exposure to unintentionally emitted carbonaceous NPs are shown in Tables 1 and 2. The mean age of the mothers was 31.0 years (standard deviation (SD): 4.7). Unexposed mothers worked longer (27.9 weeks, SD: 7.3) than exposed mothers (26.0 weeks, SD: 9.3) during pregnancy. The percentage of newborns who were SGA was 10.6. The proportion of infants who were SGA was significantly higher for the exposed group than the other groups. The mean HC of children at birth was 34.4 cm (SD: 1.4). There was no significant difference in HC between exposure groups. The monthly household income, area of residence, smoking status,

maternal education, and duration of work during pregnancy were significantly different depending on the exposure group.

The occupations held by the mothers exposed to unintentionally emitted carbonaceous NPs during pregnancy are shown in Table 3. Among the most highly exposed mothers, approximately 25% were “cooks”, 18% were “commercial travelers and manufacturing agents”, 9% were “motor vehicle drivers”, 7% were “technical salesmen and service advisers”, and 7% were “working proprietors (catering and lodging services)”.

In the multivariate analyses, mothers occupationally exposed to unintentionally emitted carbonaceous NPs during pregnancy had a higher risk of SGA than unexposed mothers (adjusted odds ratio (OR<sub>adj</sub>) = 1.80; 95% CI (1.29, 2.46)). Among the occupationally exposed mothers (n = 425), the frequency-weighted duration of work during pregnancy was not significantly associated with SGA (OR<sub>adj</sub> = 1.02; 95% CI (0.96, 1.08)) (Table 4).

Depending on whether mothers stopped working during pregnancy, the risk was significant when they stopped working during the third (OR<sub>adj</sub>=1.80; 95% CI: 1.10, 2.95) or second trimester (OR<sub>adj</sub>=1.84; 95% CI: 1.13, 3.02). This risk was not significant when the mother stopped working during the first trimester of pregnancy (Table 5).

In the adjusted analysis, there was no significant difference in HC between children born to occupationally-exposed mothers and those born to non-exposed mothers ( $\beta$  = -0.06,  $p$  = 0.173). Within the exposed group, the mean HC decreased significantly by 0.04 cm when the duration of work weighted by frequency of exposure increased by one week, adjusted for other variables ( $\beta$  = -0.04,  $p$  = 0.019) (Table 6). The associations remained non-significant if the analyses were performed considering the trimester of pregnancy during which the mothers stopped working (Table 7).

In the longitudinal data analysis (Table 8), the increase in HC over time was not significantly lower for the exposed *versus* unexposed groups ( $\beta$  = -0.0004,  $p$  = 0.5593). There was also no association ( $\beta$  = -0.002,  $p$  = 0.1314) in the analysis conducted only on the exposed group, regardless of the trimester of pregnancy when the mothers stopped working (Table 9).

The results of the multiple imputation analyses were approximately the same as those of the main analyses (Supplementary Tables 1 and 2).

#### 4. Discussion

This study shows a significant association between maternal occupational exposure to unintentionally emitted carbonaceous NPs and SGA at birth for mothers who stopped working during the second or third trimester. There was no significant association between maternal probability of exposure to unintentionally emitted carbonaceous NPs and HC but we found a slight decrease in HC at birth associated with the frequency-weighted duration of work.

In our first study conducted in 2019, we demonstrated a significant association between maternal occupational exposure to unintentional NPs and SGA (Manangama et al. 2019), without specifying the chemical composition of the particles. Here, we show an association with maternal exposure to unintentional carbonaceous NPs; the adjusted odds ratios were slightly higher than those when considering any particles, without specifying the chemical composition. To date, there are no other data available on ultrafine particles and birth weight. However, data on coarser particles (PM<sub>10</sub>) in the occupational setting and on fine particulate matter (PM<sub>2.5</sub>) in ambient air pollution are available and consistent with our findings. A nationwide cohort study conducted in Sweden showed a significant association between maternal occupational exposure to combustion products (polycyclic aromatic hydrocarbons and diesel) and SGA (Norlen et al. 2019). This is consistent with our results, given that air pollution compounds from combustion processes are largely composed of ultrafine particles. Exposure to carbonaceous particles in ambient air pollution has been shown to be associated with reduced birth weight in several studies (Basu et al. 2014; Bell et al. 2010; Ebisu and Bell 2012; Laurent et al. 2014; Laurent et al. 2016; Wilhelm et al. 2012). Based on a literature review, the recent expert report published by the French agency ANSES (Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail) suggested an effect of carbonaceous particles on low birth weight. However, the number of studies on this subject is still limited (ANSES 2019).

In our sub-analysis of whether mothers stopped working during the first, second, or third trimester of pregnancy, the adjusted odds ratios were significant for the second and third trimesters, whereas the association was not significant for the first trimester. Adverse effects on fetal growth have also been shown to be greater following exposure to PM during the second or third trimesters of pregnancy (Clemens et al. 2017; Lamichhane et al. 2018). In 2016, Laurent *et al.* showed a significant association between exposure to elemental carbon during the third trimester of pregnancy and low birth weight in term newborns (Laurent et al. 2016). These results suggest that the placental compensation mechanisms that normally develop during mid-gestation had become insufficient to maintain optimal fetal development through the full term, possibly affecting fetal weight (Coan et al. 2011). In addition, mothers working up to the second or third trimesters are exposed much longer than others. However, our results for mothers who stopped working during the first trimester should be interpreted with caution due to the small number of subjects in this category.

Concerning HC, there was no significant association with maternal occupational exposure to unintentionally emitted carbonaceous NPs during pregnancy, despite stratification by the first, second, and third trimesters. There have been no published epidemiological studies that have explored the effect of NPs on HC development. The absence of an association between maternal exposure to unintentional carbonaceous NPs and HC could be explained by the fact that, because the brain is a major consumer of oxygen, it is favored at the expense of fetal growth, which slows if the placenta is unable to provide the required amount of oxygen for development or during a fetal hypoxia (Ducsay et al. 2018; Giussani 2016; Guihard-Costa 1993). This phenomenon has been observed in other species with large brains (primates), and could explain the lack of an effect or a low effect on HC when there is an effect on gestational weight (Guihard-Costa 1993). These results could also be explained by the fact that the Elfe cohort includes only children born at 33 weeks or more of gestation, with the possibility of selecting less-sick children, with the sickest being excluded. A large-scale European study on maternal exposure to PM and the development of HC, including newborns from 22 weeks of gestation, showed a significant effect (Pedersen et al. 2016). This partially reinforces our hypothesis on the selection of our study sample, which could have led to an underestimation of the effect.

Furthermore, possible errors in the measurement of HC of infants included in our study, subject to variability depending on the person measuring it, could have led to an underestimation of the effect. Indeed, it was not the same person who measured the HC between children nor the same person between the visits of each child. Thus, a non-standardized measurement was used. There was also no significant effect of prenatal exposure to carbonaceous NPs on HC at two years of age. Indeed, literature data have shown that the HC of children born with a small HC may catch up over time (Brandt 1976, 1981; Soesanti et al. 2019).

Here, we focused on carbonaceous particles emitted during work processes because the occupational activities of participants of our study (described in Table 3) correspond mainly to exposure from the combustion of organic matter, which leads to carbonaceous particle emission. Moreover, published data suggest that ultrafine particles emitted in occupational settings are generated mainly following combustion processes (Manigrasso et al. 2019), primarily generating carbonaceous particles in high amounts (Baraniecka et al. 2010; Leoni et al. 2016; Morawska and Zhang 2002; Paul et al. 2013). Toxicological data have shown that carbonaceous nanoparticles show biological reactivity for certain tissues (Lam et al. 2006; van Berlo et al. 2014), including those of the placenta (Campagnolo et al. 2013; Detmar et al. 2008; Qi et al. 2014). Indeed, carbonaceous particles, specifically black carbon coming from combustion-derived PM, were found, for the first time, in the placentas of women exposed in real-life conditions during their pregnancy (Bové et al. 2019). This provides a potential mechanism to explain the adverse effects of carbonaceous particles on pregnancy and offspring. The results of the few existing epidemiological studies on ambient PM<sub>2.5</sub> of elemental carbon have shown a significant association with low birth weight (Bell et al. 2010; Ebisu and Bell 2012; Laurent et al. 2014; Pedersen et al. 2013; Wilhelm et al. 2012). In the occupational setting, certain occupations described in our study may have exposed mothers to chemical families of NPs other than carbonaceous particles. Nevertheless, as mentioned above, the participants selected in our study were mainly exposed to carbonaceous NPs.

Individual data on extra-occupational exposure to particulate matter from ambient air pollution (PM<sub>2.5</sub>) that could have been used as adjustment factors are not yet available for the Elfe cohort. However, we

used other relevant variables (the area of residence, socio-economic status) to account for potential confounding factors.

Occupational exposure attracted our particular attention because it has been shown that concentrations of UNPs generated by work processes can be much higher than ambient levels (Viitanen et al. 2017). A recent literature review showed that exposure to ultrafine particles is higher in the workplace than in the non-professional environment (Viitanen et al. 2017).

The version of the job exposure matrix that we used (MatPUF) has not yet integrated the intensity parameter. Thus, it was not possible to examine dose-response relationships, which was one of the limitations of our study. Thus, we could not assess the effects associated with high or low intensity exposure, only those associated with a longer duration of exposure. In addition, the MatPUF identified homogeneous groups of exposure defined by the occupation held by mothers during pregnancy, without considering inter-individual differences. This could have led to non-differential misclassification and under-estimation of the association (Burstyn et al. 2014). However, this retrospective assessment method, based on a job exposure matrix, prevents recall bias concerning the characterization of the exposure by participants. This matrix, based on expert opinion, also allowed us to characterize the chemical type of the particles to which the mothers were occupationally exposed during pregnancy, without having to question participants, which could have been a source of bias.

We performed our analyses on complete data, excluding subjects with missing data for the variables of interest (SGA, HC, and adjustment variables). Supplemental analyses using the whole dataset by multiple imputation (MICE) showed that subject selection in our main analyses did not likely influence our results.

## 5. Conclusion

This study shows a significant effect of exposure to unintentionally emitted carbonaceous NPs on SGA, depending on the period of exposure during pregnancy. These results are consistent with those that have been previously published on PM from air pollution. Preventive measures that account for the different periods of exposure during pregnancy may be necessary in the workplace. Further studies

should be conducted using other measurement methods to confirm this effect or should also consider overall occupational and extra-occupational exposure to carbonaceous NPs.

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### **Competing financial interests declaration**

All authors declare they have no actual or potential competing financial interest.

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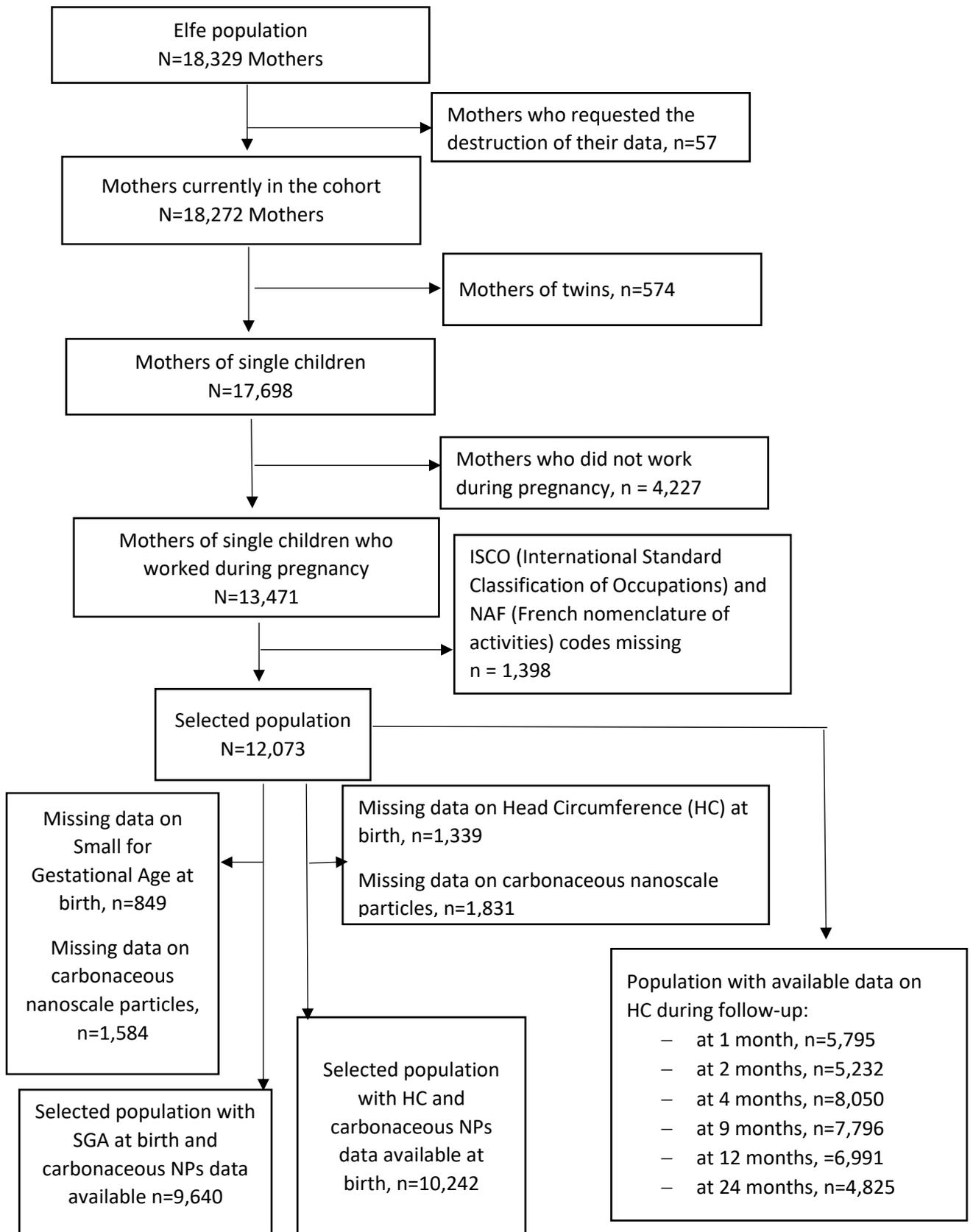


Fig. 1. Flow chart for the selection of the final population analyzed in the study on occupational exposure to NPs and SGA, Elfe Cohort, Metropolitan France, 2019.

Table 1. Characteristics of the participants depending on exposure status. Quantitative variables. N=10,242, Elfe sub-study on occupational exposures to carbonaceous nanoscale particles unintentionally emitted, Metropolitan France, 2019.

	Total (n= 10,242)		Unexposed (n=8,361)		Uncertain (n=1,423)		Exposed (n= 458)		p-value*
	mean	± SE	mean	± SE	mean	±S E	mean	± SE	
Maternal age (years)	31.0	± 4.7	31.2	± 4.5	30.2	± 5.1	30.4	± 5.1	<b>&lt;.0001</b>
Time worked during pregnancy (weeks)	27.4	± 7.9	27.9	± 7.3	26.1	± 8.6	26.0	± 9.3	<b>&lt;.0001</b>
Head circumference at birth (cm)	34.4	± 1.4	34.4	± 1.4	34.4	± 1.5	34.4	± 1.4	0.5533
Gestational age (weeks of gestation)	39.3	± 1.4	39.3	± 1.4	39.2	± 1.4	39.4	± 1.5	<b>0.0178</b>
Child birth weight (g)	3,340	± 470	3,340	± 460	3,340	± 500	3,320	± 480	0.5759

\**Kruskall-Wallis test to compare quantitative variables; 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 more than 50%.*

Table 2. Characteristics of the participants depending on exposure status. Qualitative variables. N=10,242, Elfe sub-study on occupational exposures to carbonaceous nanoscale particles unintentionally emitted, Metropolitan France, 2019.

	Total (n= 10,242)		Unexposed (n=8,361)		Uncertain (n=1,423)		Exposed (n=458)		p- value*
	n	(%)	n	(%)	n	(%)	n	(%)	
Small for gestational age									<b>0.0035</b>
Yes	1,083	(10.6)	848	(10.1)	169	(11.9)	66	(14.4)	
No	9,159	(89.4)	7,513	(89.9)	1,254	(88.1)	392	(85.6)	
Maternal education**									<b>&lt;.0001</b>
University	7,116	(69.8)	6,339	(76.2)	543	(38.3)	234	(51.2)	
High school	1,818	(17.8)	1,286	(15.5)	405	(28.5)	127	(27.8)	
Lower	1,265	(12.4)	698	(8.3)	471	(33.2)	96	(21.0)	
Smoking during pregnancy **									<b>&lt;.0001</b>
No	7,677	(75.8)	6,426	(77.8)	946	(67.0)	305	(66.9)	
Yes	2,455	(24.2)	1,839	(22.2)	465	(33.0)	151	(33.1)	

High blood pressure **									0.3002
No	9,635	(96.7)	7,859	(96.7)	1,340	(96.2)	436	(98.2)	
Yes	329	(3.3)	268	(3.3)	53	(3.8)	8	(1.8)	
Child's sex									0.5075
1-Male	5,186	(50.6)	4,221	(50.5)	721	(50.8)	244	(53.3)	
2-Female	5,052	(49.4)	4,139	(49.5)	699	(49.2)	214	(46.7)	
Residential area									<b>0.0170</b>
Rural	295	(2.9)	228	(2.7)	43	(3.0)	24	(5.2)	
Semi-urban	3,384	(33.0)	2,755	(33.0)	473	(33.2)	156	(34.1)	
Urban	6,562	(64.1)	5,377	(64.3)	907	(63.8)	278	(60.7)	
Monthly household income (euros)**									<b>&lt;.0001</b>
>4,100	2,466	(24.6)	2,137	(26.0)	251	(18.3)	78	(17.7)	
2,500 to 4,100	5,632	(56.2)	4,814	(58.6)	608	(44.2)	210	(47.7)	
1 to 2,500	1,926	(19.2)	1,258	(15.4)	516	(37.5)	152	(34.6)	

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\* Chi-square or Fisher test; \*\* analysis of available data; missing data on monthly household income (n=218), smoking status during pregnancy (n=110), maternal education (n=43), high blood pressure (n=278)

Table 3. The exposing jobs (jobs with probability of exposure to carbonaceous nanoscale particles unintentionally emitted > 50%), among exposed mothers (N=458)

Exposing jobs	N	(%)	Probability of exposure
Cook	114	(24.89)	0.83
Commercial travellers and Manufacturers' agents	83	(18.12)	0.75
Motor vehicle drivers	39	(8.52)	0.75
Technical salesmen and service advisers	33	(7.21)	0.75
Working proprietors (catering and lodging services)	32	(6.99)	0.75
Specialised farmers	24	(5.24)	0.94
Bakers, pastrycooks and confectionery makers	23	(5.02)	0.83
Street vendors, canvassers and newsvendors	14	(3.06)	0.75
Orchard, vineyard and related tree and shrub crop workers	14	(3.06)	0.94
Livestock workers	11	(2.40)	0.96
Nursery workers and gardeners	11	(2.40)	0.94
Field crop and vegetable farm workers	8	(1.75)	0.94
Chemists	6	(1.31)	0.75
Civil engineering technicians	6	(1.31)	0.99
Managers (Catering and lodging services)	5	(1.09)	0.75
General farmers	5	(1.09)	0.94
Mechanical engineers	3	(0.66)	0.92
Fire-fighters	3	(0.66)	0.83
Agricultural and animal husbandry workers not elsewhere classified	3	(0.66)	0.94
Jewellery and precious metal workers	3	(0.66)	0.99

Physical science technicians	2	(0.44)	0.75
Chemical engineers	2	(0.44)	0.60
Farm managers and supervisors	2	(0.44)	0.75
Production supervisors and general foremen	2	(0.44)	0.99
Civil engineers	1	(0.22)	0.53
Metallurgists	1	(0.22)	0.96
Aircraft pilots, navigators and flight engineers	1	(0.22)	0.91
General farm workers	1	(0.22)	0.94
Poultry farm workers	1	(0.22)	0.83
Forestry workers (except logging)	1	(0.22)	0.83
Machinery fitters and machine assemblers	1	(0.22)	0.99
Motor vehicle mechanics	1	(0.22)	0.99
Sheet-metal workers	1	(0.22)	0.99
Glass formers, cutters, grinders and finishers	1	(0.22)	0.99

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Table 4. Association between maternal occupational exposures to carbonaceous nanoscale particles unintentionally emitted and small for gestational age. N=9,640, sub-study Elfe, Metropolitan France, 2019.

	N	ORadj (95% CI)	P
Occupational exposures to carbonaceous NPs			<b>&lt;.0001</b>
Unexposed	7,879	Ref	
Uncertain (>0-50%)	1,336	<b>1.39 (1.12, 1.74)</b>	
Exposed (>50%)	425	<b>1.80 (1.29, 2.46)</b>	
Frequency-weighted duration of work (/days)			
Exposed (>50%)	425	1.02 (0.96, 1.08)	0.4708

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.

Table 5. Association between maternal occupational exposures to carbonaceous nanoscale particles unintentionally emitted and small for gestational age, depending on whether mothers stopped working during pregnancies (first, second or third trimester). N=9,640, sub-study Elfe, Metropolitan France, 2019

	Stopped during 1 <sup>st</sup> trimester			Stopped during 2 <sup>nd</sup> trimester			Stopped during 3 <sup>rd</sup> trimester		
	N	ORadj (95% CI)	P	N	ORadj (95% CI)	p	N	ORadj (95% CI)	p
Occupational exposures to carbonaceous NPs			0.4744			<b>0.0068</b>			<b>0.0117</b>
Unexposed	611	Ref		3,412	Ref		3,856	Ref	
Uncertain (>0-50%)	186	1.02 (0.53, 1.97)		557	<b>1.49 (1.07, 2.07)</b>		593	<b>1.45 (1.04, 2.04)</b>	
Exposed (>50%)	66	1.71 (0.71, 4.12)		168	<b>1.84 (1.13, 3.02)</b>		193	<b>1.80 (1.10, 2.95)</b>	

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.

Table 6. Association between maternal occupational exposures to carbonaceous nanoscale particles unintentionally emitted and head circumference at birth. Multivariate linear regression. N=10,242 sub-study Elfe, Metropolitan France, 2019.

	n	Coef	CI 95%	p*
<b>Occupational exposures to carbonaceous NPs</b>				
Unexposed	8,361	Ref		
Uncertain (>0-50%)	1,423	0.02	(-0.07, 0.09)	0.707
Exposed (>50%)	458	-0.06	(-0.30, 0.17)	0.173
<b>Frequency weighted duration of work (/week)</b>				
Exposed (>50%)	458	<b>-0.04</b>	<b>(-0.07, -0.01)</b>	<b>0.019</b>

Adjusted for smoking, residential areas, maternal education, high blood pressure during pregnancy, gestational diabetes, and child' sex and gestational age; p\* p-value (Chi2 of Wald test); ORadj: adjusted odds ratio; CI: confidence interval; N: number; In bold, statistically significant associations.

Table 7. Association between maternal occupational exposures to carbonaceous nanoscale particles unintentionally emitted and head circumference at birth, depending on whether mothers stopped working during her pregnancy (first, second or third trimester). N=10,242, sub-study Elfe, Metropolitan France, 2019

	Stopped during 1 <sup>st</sup> trimester			Stopped during 2 <sup>nd</sup> trimester			Stopped during 3 <sup>rd</sup> trimester		
	N	Coef (95% CI)	p	N	Coef (95% CI)	p	N	Coef (95% CI)	p
Occupational exposures to carbonaceous NPs									
Unexposed	672	Ref		2,628	Ref		5,061	Ref	
Uncertain (>0-50%)	192	-0.14 (-0.42, 0.13)	0.30	490	-0.01 (-0.17, 0.14)	0.824	741	0.03 (-0.08, 0.14)	0.653
Exposed (>50%)	80	0.12 (-0.26, 0.49)	0.54	131	0.02 (-0.24, 0.28)	0.897	247	-0.04 (-0.22, 0.14)	0.657

Adjusted for smoking, residential areas, maternal education, high blood pressure during pregnancy, gestational diabetes, child' sex and gestational age; p\*

p-value (Chi2 of Wald test); ORadj: adjusted odds ratio; CI: confidence interval; N: number;

In bold: statistically significant associations.

Table 8. Variation in head circumference from birth to two years olds of children born from mothers occupationally exposed to carbonaceous nanoscale particles unintentionally emitted during pregnancy. N=10,242, sub-study Elfe, Metropolitan France, 2019

	n	Coef	p*
<b>Occupational exposures to carbonaceous NPs</b>			
Unexposed	8,361	Ref	
Uncertain (>0-50%)	1,423	0.00029	0.5227
Exposed (>50%)	458	-0.0004	0.5593
<b>Log(Frequency weighted duration of work)</b>			
Exposed (>50%)	458	-0.002	0.1314

Adjusted for parental smoking status, household income, maternal education, residential area, child's sex and log of age during follow-up; p\* p-value (Chi2); Coef: regression coefficient; N: number.

Table 9. Variation in head circumference from birth to two years olds of children born from mothers occupationally exposed to carbonaceous nanoscale particles unintentionally emitted during pregnancy, depending on whether mothers stopped working during her pregnancy (first, second or third trimester). N=10,242, sub-study Elfe, Metropolitan France, 2019

	Stopped during 1 <sup>st</sup> trimester			Stopped during 2 <sup>nd</sup> trimester			Stopped during 3 <sup>rd</sup> trimester		
	N	Coef	p	N	Coef	p	N	Coef	p
Occupational exposures to carbonaceous NPs									
Unexposed	672	Ref		2,628	Ref		5,061	Ref	
Uncertain (>0-50%)	192	0.002	0.3745	490	0.001	0.4987	741	-0.001	0.8172
Exposed (>50%)	80	0.003	0.2548	131	-0.003	0.0860	247	-0.001	0.8869

Adjusted for parental smoking status, household income, maternal education, residential area, child's sex and log of age during follow-up; p\* p-value

(Chi2); Coef: regression coefficient; N: number.