



# Multiple maternal occupational exposures during pregnancy and intrauterine growth: analysis of the French Longitudinal Study of Children - ELFE cohort, using data-driven approaches

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## ARTICLE INFO

### Keywords:

Occupational exposome  
Intrauterine growth  
Pregnancy  
EWAS  
LASSO  
Random forest

## ABSTRACT

**Objective:** To use data-driven approaches to investigate maternal multi-occupational exposures during pregnancy and their effects on intrauterine growth.

**Methods:** Maternal occupational exposure to 47 factors during pregnancy was evaluated with job-exposure matrices in the French ELFE cohort. The outcomes of interest were birthweight (BW), small for gestational age (SGA) and head circumference (HC). Occupational exposures associated with these outcomes were identified by EWAS, LASSO, and random forest. The five exposures with the strongest effects selected with these approaches were included in a final multivariate model with significant interactions.

**Results:** We included 12,851 women. The most important occupational factors predictive of SGA were endocrine disruptors, high strain, kneeling/squatting, job demands, physical effort. No significant associations were detected when these variables were combined in a final model. For BW, the most important variables were leaning forward/sideways, using a computer screen, ultrafine particles, physical effort, airborne germs, repetitive actions. The use of a computer screen significantly decreased BW and, for women not exposed to airborne germs,

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leaning forward/sideways significantly increased BW. For HC, repetitive actions, oxygenated solvents, kneeling/squatting, airborne germs, working outdoors were the most important predictive factors. Repetitive actions and working outdoors significantly decreased HC. HC also decreased in women exposed to both airborne germs, and oxygenated solvents. Similar results were found for women who worked during the third trimester.

**Conclusion:** Our findings highlight potential roles of chemical, biological and postural factors and their interactions in determining intrauterine growth. These results highlight the importance of considering multiple exposures in occupational health studies.

## 1. Introduction

A study of 13 European birth cohorts showed that 80.2 % of women work during pregnancy (Casas et al., 2015). A large proportion of these women may be exposed to various occupational factors of a chemical, physical, biological, strenuous, organizational or psychosocial nature. Simultaneous exposure to multiple factors may also be frequent. For example, the results of the French national occupational health survey conducted in 2014 indicated that over 40 % of pregnant mothers were exposed to at least three potential occupational risk factors during pregnancy, and about 30 % were exposed to at least five risk factors (Henrotin et al., 2018). Moreover, a previous study showed that women were exposed to a median of 6 occupational factors during pregnancy (Tartaglia et al., 2024). Occupational exposure to certain factors during pregnancy has been associated with intrauterine growth retardation and, in particular, with infants being born small for gestational age (SGA) (Cai et al., 2020; Croteau, 2020; Rekha et al., 2023; Ulin et al., 2024), with a low birthweight (BW) (Cai et al., 2020; Croteau, 2020; Rekha et al., 2023; Ulin et al., 2024; Bonzini et al., 2007; Palmer et al., 2013) or small head circumference (HC) (Cai et al., 2020; Croteau, 2020; Rekha et al., 2023; Ulin et al., 2024).

Most studies of the relationship between occupational exposures and intrauterine growth to date have focused on only one or a small number of occupational exposures (Cai et al., 2020; Croteau, 2020; Rekha et al., 2023; Ulin et al., 2024; Bonzini et al., 2007; Palmer et al., 2013), analyzed by linear and logistic regression techniques. However, such models are subject to limitations in handling multiple and correlated exposures, which may yield unstable parameter estimates with large standard errors (Stafoggia et al., 2017). Furthermore, it is not possible to consider confounding and interactive effects involving multiple exposures in single-exposure studies. More advanced statistical methods are, therefore, required for studies of the complex associations between multiple exposures and intrauterine growth.

Different methods were identified, according to the research question (Joubert et al., 2022), which can be to estimate the overall effect of the mixture, to identify exposures associated with the outcome, to identify most important exposures associated with the outcome, to determine specific exposure patterns, to study the association between an outcome and a priori defined groups of exposure. Data-driven approaches based on machine learning can address some of these issues, and in particular that of identification of most important exposures associated with the outcome. Several studies have compared the performance of different machine-learning models for the identification of associations between the exposome and health (Agier et al., 2016; Barrera-Gómez et al., 2017; Lenters et al., 2018; Sun et al., 2013). These studies have failed to identify any single model as universally better. Various methods can be used to address different questions. They can be classified into three groups, as shown by Stafoggia et al.: (1) dimension reduction, (2) variable selection, and (3) clustering (Stafoggia et al., 2017). It is possible to combine different methods to increase the likelihood of capturing different aspects of the relationships between occupational exposure and intrauterine growth, including interactions between factors, facilitating a pluralist approach to data interpretation (Stafoggia et al., 2017). We used two variable selection approaches (Exposome-wide association study – EWAS, and least absolute shrinkage and selection operator – LASSO) and one clustering approach (random

forest) to take advantage of the strengths of these different methods and compensate for their limitations. Variable selection is an alternative to dimension reduction that can decrease complexity and the risk of redundancy. EWAS can identify analytically important exposure-outcome pairs across all measured exposures (Chung et al., 2024). LASSO is a penalized regression technique particularly useful for high-dimensional data with many potential predictors (Tibshirani, 1996). The random forest approach is non-parametric and can be used to capture complex interactions and patterns within the data (Stafoggia et al., 2017; 4).

The objective of this study was to explore multiple maternal occupational exposures during pregnancy and their relationship to intrauterine growth, through a combination of these three data-driven approaches.

## 2. Methods

### 2.1. Population study

The French Longitudinal Study of Children (ELFE) cohort is the first French national study dedicated to monitoring participants from birth to adulthood. The methodology of the ELFE cohort has been described in detail elsewhere (Charles et al., 2020). Briefly, maternity hospitals were selected based on a two-stage stratified random sampling plan. First, maternity wards located in metropolitan France were randomly selected at the national level from a sampling base stratified by the institution's status (private/public) and according to the number of births per year and region. Recruitment took place within 320 French maternity departments in 2011. Single or multiple live births at  $\geq 33$  weeks of gestation (premature babies  $>33$  weeks of gestation are included in the study), for which the mothers were  $\geq 18$  years old, did not plan to leave France within three years and had signed an informed consent form, were included in the ELFE cohort. Overall, 18,270 children were followed up in this cohort.

For this study, we excluded multiples pregnancies ( $n = 574$ ), pregnancies resulting in neonates with major congenital malformation ( $n = 377$ ) as defined by the European surveillance system for congenital abnormalities ("European Platform for Rare Disease Registration"), and mothers who did not work during their pregnancies ( $n = 4137$ ) (Appendix C).

The ELFE study was approved by the Consultative Committee for the Treatment of Information in Health Research (CCTIRS), the National Commission for Data Protection and Liberties (CNIL), and the competent ethics committee (CPP - Committee for the Protection of Persons). The study was also approved by the National Council for Statistical Information (CNIS).

### 2.2. Data collection

Sociodemographic data were collected by face-to-face interviews at the maternity unit and medical data were collected from medical records. Information about the occupations of the women during pregnancy, including job title, was collected during the face-to-face interviews, which took place during the women's stay in the maternity unit after the delivery, and through an additional questionnaire completed two months after the delivery. Additional details can be

obtained from: <https://www.elfe-france.fr/en>.

### 2.3. Assessment of occupational exposure

The occupational exposures investigated here were characterized with job-exposure matrices (JEMs) linked to the jobs of the mothers based on a common job coding system. All mothers included in this study held only one job during their pregnancy. Participant-reported jobs were coded by one expert, according to the International Standard Classification of Occupations (ISCO-1968) and the French classification of professions and socioprofessional categories (PCS-2003). Industry activities were coded according to the International Standard Industrial Classification of All Economic Activities (ISIC-1975) and the French nomenclature of activities (NAF-2003). We used 12 JEMs and one database to evaluate the occupational exposures of the pregnant women (Table 1). We selected general population JEMs, preferably from the French (or European or North American) population, and characterizing the exposure close to 2011. JEM selected to be applied in our population study included at least one type of occupational exposure that has been suspected to have a potential effect on reproduction (fertility issues, malformations, intrauterine growth) (Teyssie et al., 2019; Certenais et al., 2019). If an occupational exposure was present in multiple JEMs, we prioritized the one developed using the French population. The description of JEMs applied to the Elfe cohort is described in Appendix A. The occupational exposures evaluated are listed in Table 1. We studied 17 chemical, 8 physical, 4 biological, 12 strenuous, 3 organizational and 3 psychosocial factors. For each type of exposure, we built a dichotomous (exposed, not exposed) categorical exposure variable based primarily on probability (0–50 %, ≥50 %) or, if the probability was unknown, intensity of exposure. The unexposed group was chosen as the reference group, for each occupational exposure of interest, that allow to be specific to the exposure of interest. Only 29 of the 47 occupational exposures characterized were included in the final analysis, because each of the other exposures concerned fewer than ten women (chlorinated and petroleum solvents, arsenic, cadmium, chromium, iron, lead, nickel, welding fumes, polycyclic aromatic hydrocarbons, benzo-a-pyrene, carbon monoxide, non-thermal intermediate frequency, radiofrequency, thermal intermediate frequency, ultraviolet).

### 2.4. Outcomes

BW is the weight of the newborn at birth, expressed in grams. SGA was defined as a BW under the 10th percentile for gestational age and sex according to WHO curves (de Onis et al., 2007; Verspyck et al., 2022). HC is the fronto-occipital circumference measured at birth, in centimeters.

### 2.5. Statistical analysis

We performed a two-step analysis.

We first ranked exposures, selecting the most important occupational exposures with three different data-driven approaches: EWAS, LASSO and random forest. A short summary of the methods used is provided below and the tuning parameters for each method are presented in appendix B.

EWAS identifies analytically important exposure-outcome pairs across all measured exposures (Chung et al., 2024). It corresponds to multiple single-exposure approaches based on logistic (for SGA) and linear (for BW and HC) regressions, depending on the outcome. The *p*-values were corrected for multiple testing with a threshold for the effective number of tests (Li et al., 2012). This method is adapted from Bonferroni correction, with an estimation of the number of truly independent tests based on the correlation structure of the exposure variables. We then divided the nominal significance by the effective number of tests calculated. The variable importance score was based on the

*p*-values obtained. The occupational exposures with the lowest *p*-values were considered to be the most important, and had a lower score.

LASSO, a penalized regression technique particularly useful for high-dimensional data with many potential predictors, selects the most important variables within a group of highly correlated variables (Stafoggia et al., 2017) by shrinking all coefficients toward zero. As LASSO is sensitive to a tuning parameter ( $\lambda$ ), the final set of variables of importance was chosen by the stability selection procedure (Hofner and Hothorn, 2021). The variable importance score was calculated according to the selection probabilities. Exposures with the highest selection probabilities were considered to be the most important and had lower scores.

The random forest approach is a non-parametric approach to classification and regression based on the aggregation of a decision tree, facilitating the capture of complex interactions and patterns within the data (Stafoggia et al., 2017; Breiman, 2001). The variable importance score was calculated from the difference between the out-of-bag (OOB) error on the perturbed OOB samples, and the initial OOB error. The most important exposures had a lower score.

For each approach, all exposures were ranked according to the importance of their contribution to the prediction of the outcome, with lower values corresponding to the most important variables. An overall ranking was then calculated, based on the median of the three ranks for a given factor (Ohanyan et al., 2022).

The final model for each outcome was constructed by including the top five occupational exposures identified for each health outcome in the exposure ranking step. We explored all potential second-term interactions between each of the selected variables, by logistic (for SGA) and linear (for BW and HC) regressions including interaction terms. The final logistic (for SGA) or linear (for BW and HC) models, thus, contained the five most important occupational exposures and potentially important interaction terms (cutoff:  $p < 0.15$ ).

Missing data on occupational exposures were imputed by a method based on chain equations with the mice package in R software to generate five tables, by five iterations. The imputation model contains all the occupational exposure variables, and all covariates.

We used a DAG (Appendix C) to adjust all models described above for educational level (low, high-school, university), pre-pregnancy BMI ( $<18.5$  kg/m<sup>2</sup>, 18.5–24.9 kg/m<sup>2</sup>, 25.0–29.9 kg/m<sup>2</sup>,  $\geq 30$  kg/m<sup>2</sup>), tobacco use (yes, no) and alcohol consumption (continuous, number of glasses per day) during pregnancy for the SGA analysis. For the BW and HC analyses, we also adjusted for gestational age (continuous) and the sex of the infant (female, male), strong determinants of intrauterine growth. These variables were not included for SGA analysis since these factors are already considered in the construction of this outcome variable.

Effect estimates are presented as odds ratios (OR) for logistic regressions and beta ( $\beta$ ) for linear regressions.

We performed a sensitivity analysis on mothers who continued working until the third trimester of pregnancy, excluding those who stopped working earlier, as this period appears to carry the highest risk for fetal growth, particularly for weight gain (Lepercq and Boileau, 2005). In humans, intrauterine fetal growth is quite slow until the 23rd week of gestation, and then accelerates before peaking around the 34th week (Lepercq and Boileau, 2005).

The analyses were performed with R Core Team (2023) software, using the packages mice (Buuren et al., 2023) for multiple imputation, rexpome (rexpome project n) for EWAS, stabs (Hofner and Hothorn, 2021) for LASSO, and VSURF (Genuer et al., 2022) for random forest.

## 3. Results

### 3.1. Population

Our study population consisted of 12,851 women (Appendix D). Comparisons between included and excluded participants are presented

**Table 1**

Assessment of maternal occupational exposures in the French National ELFE cohort.

| Factors                                                                                                                                                | Job exposure matrix or database                                    | Construction              | Occupation nomenclatures                       | Industry activities nomenclatures | Metrics                               | Temporal axis/Gender-specific | Exposure parameter used in analyses                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|---------------------------|------------------------------------------------|-----------------------------------|---------------------------------------|-------------------------------|------------------------------------------------------------------------------------|
| <b>1) Chemical factors</b>                                                                                                                             |                                                                    |                           |                                                |                                   |                                       |                               |                                                                                    |
| Chlorinated solvents <sup>a,e</sup>                                                                                                                    | Matgéné – chlorinated solvents France (Dananché and Fèvotte, 2009) | Experts                   | ISCO-1968<br>PCS-1994                          | NAF-1993                          | Probability<br>Frequency<br>Intensity | Yes<br>1950–2007/<br>No       | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |
| Oxygenated solvents <sup>b</sup>                                                                                                                       | Matgéné – oxygenated solvents France (Dananché et al., 2015)       | Experts                   | ISCO-1968<br>PCS-1994                          | NAF-1993                          | Probability<br>Frequency<br>Intensity | Yes<br>1950–2012/<br>No       | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |
| Petroleum solvents <sup>c,e</sup>                                                                                                                      | Matgéné – petroleum solvents France (Pilorget et al., 2007)        | Experts                   | ISCO-1968<br>PCS-1994                          | NAF-1993                          | Probability<br>Frequency<br>Intensity | Yes<br>1947–2005/<br>No       | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |
| Detergents                                                                                                                                             | FinJEM<br>Finland (Kauppinen et al., 2014)                         | Experts                   | ISCO-1988                                      | –                                 | Probability<br>Intensity              | Yes<br>1995–2009/<br>No       | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |
| Pesticides                                                                                                                                             | Pestipop<br>France (Carles et al., 2018)                           | Experts<br>Questionnaires | PCS-2003                                       | NAF-2003                          | Probability<br>Frequency              | No/No                         | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |
| Heavy metals<br>Arsenic <sup>e</sup><br>Cadmium <sup>e</sup><br>Chromium <sup>e</sup><br>Iron <sup>e</sup><br>Lead <sup>e</sup><br>Nickel <sup>e</sup> | FinJEM<br>Finland (Kauppinen et al., 2014)                         | Experts                   | ISCO-1988                                      | –                                 | Probability<br>Intensity              | Yes<br>1995–2009/<br>No       | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |
| Ultrafine particles                                                                                                                                    | MatPUF<br>France (Audignon-Durand et al., 2021)                    | Experts                   | ISCO-1968                                      | NAF-1993                          | Probability<br>Frequency              | Yes<br>1950–2014/<br>No       | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |
| Welding fumes <sup>e</sup>                                                                                                                             | FinJEM<br>Finland (Kauppinen et al., 2014)                         | Experts                   | ISCO-1988                                      | –                                 | Probability<br>Intensity              | Yes<br>1995–2009/<br>No       | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |
| Polycyclic aromatic hydrocarbon <sup>f</sup><br>Benzo-a-pyrene <sup>e</sup>                                                                            | FinJEM<br>Finland (Kauppinen et al., 2014)                         | Experts                   | ISCO-1988                                      | –                                 | Probability<br>Intensity              | Yes<br>1995–2009/<br>No       | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |
| Gas<br>Carbon monoxide <sup>e</sup>                                                                                                                    | FinJEM<br>Finland (Kauppinen et al., 2014)                         | Experts                   | ISCO-1988                                      | –                                 | Probability<br>Intensity              | Yes<br>1995–2009/<br>No       | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |
| Endocrine disruptor <sup>d</sup>                                                                                                                       | EDC<br>United Kingdom (Brouwers et al., 2009)                      | Experts                   | ISCO-1988                                      | –                                 | Probability                           | No/No                         | Not exposed:<br>probability between<br>0 and 10 %<br>Exposed: probability<br>>10 % |
| <b>2) Physical factors</b>                                                                                                                             |                                                                    |                           |                                                |                                   |                                       |                               |                                                                                    |
| Ionizing radiation                                                                                                                                     | CANJEM<br>Canada (Sauvé et al., 2018)                              | Experts                   | ISCO-1968<br>CCDO-1971<br>NOC-2011<br>SOC-2010 | –                                 | Probability<br>Intensity<br>Frequency | Yes<br>1920–2005/<br>No       | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |
| Low-frequency magnetic fields                                                                                                                          | FinJEM<br>Finland (Kauppinen et al., 2014)                         | Experts                   | ISCO-1988                                      | –                                 | Probability<br>Intensity              | Yes<br>1995–2009/<br>No       | Not exposed:<br>probability between<br>0 and 50 %<br>Exposed: probability<br>>50 % |

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Table 1 (continued)

| Factors                                                                                                                                    | Job exposure matrix or database                                                           | Construction                                                                      | Occupation nomenclatures | Industry activities nomenclatures | Metrics                 | Temporal axis/Gender-specific | Exposure parameter used in analyses                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------|-----------------------------------|-------------------------|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Non-thermal intermediate frequency (IFELF) <sup>e</sup><br>Radiofrequency (RF) <sup>e</sup>                                                | RF-JEM<br>France, UK, New Zealand, Germany, Israel, USA and Canada (Migault et al., 2019) | Literature-based measurement data and study participant questionnaire information | ISCO-1988                | –                                 | Probability Intensity   | Yes<br>1974–2013/<br>No       | Not exposed: probability between 0 and 50 %<br>Exposed: probability >50 %                                                                                                                                                                                                                                         |
| Thermal intermediate frequency (IFRF) <sup>e</sup><br>Ultraviolet <sup>e</sup>                                                             | FinJEM<br>Finland (Kauppinen et al., 2014)                                                | Experts                                                                           | ISCO-1988                | –                                 | Probability Intensity   | Yes<br>1995–2009/<br>No       | Not exposed: probability between 0 and 50 %<br>Exposed: probability >50 %                                                                                                                                                                                                                                         |
| <b>3) Biological factors</b>                                                                                                               |                                                                                           |                                                                                   |                          |                                   |                         |                               |                                                                                                                                                                                                                                                                                                                   |
| Airborne germs                                                                                                                             | Mat O Covid<br>France (Descatha et al., 2021)                                             | Experts                                                                           | PCS-2003<br>ISCO-2008    | –                                 | Probability             | No/No                         | Not exposed: probability between 5 and 50 %<br>Exposed: probability >50 %                                                                                                                                                                                                                                         |
| Cytomegalovirus, parvovirus B19<br>Hepatitis A, E<br>Hepatitis B, C, HIV                                                                   | Eficatt <sup>f</sup><br>France (Base de données EFICATT)                                  | Experts                                                                           | ISCO-1968                | –                                 | Exposed/<br>Not exposed | No/No                         | Not exposed<br>Exposed                                                                                                                                                                                                                                                                                            |
| <b>4) Physically strenuous factors</b>                                                                                                     |                                                                                           |                                                                                   |                          |                                   |                         |                               |                                                                                                                                                                                                                                                                                                                   |
| Strength<br>Intensity of physical effort<br>Carrying loads 10–25 kg<br>Handling of loads >4 kg                                             | JEM Constances<br>France (Evanoff et al., 2019)                                           | Questionnaires                                                                    | PCS-2003                 | –                                 | Bias-corrected mean     | No/No                         | <u>For intensity of physical efforts:</u><br>Not exposed: no physical effort, extremely light, very light, light<br>Exposed: slightly difficult, challenging, very difficult, extremely difficult, exhausting<br><u>For others factors:</u><br>Not exposed: almost never, rarely<br>Exposed: often, almost always |
| Work posture<br>Arms held up above the shoulders<br>Standing<br>Kneeling or squatting<br>Leaning forward or sideways<br>Repetitive actions | JEM Constances<br>France (Evanoff et al., 2019)                                           | Questionnaires                                                                    | PCS-2003                 | –                                 | Bias-corrected mean     | No/No                         | <u>For intensity of physical efforts:</u><br>Not exposed: no physical effort, extremely light, very light, light<br>Exposed: slightly difficult, challenging, very difficult, extremely difficult, exhausting<br><u>For others factors:</u><br>Not exposed: almost never, rarely<br>Exposed: often, almost always |
| Vibrations<br>Using vibrating tools<br>Driving construction machinery<br>Driving a vehicle<br>Using a computer screen or control panel     | JEM Constances<br>France (Evanoff et al., 2019)                                           | Questionnaires                                                                    | PCS-2003                 | –                                 | Bias-corrected mean     | No/No                         | <u>For intensity of physical efforts:</u><br>Not exposed: no physical effort, extremely light, very light, light<br>Exposed: slightly difficult, challenging, very difficult, extremely difficult, exhausting<br><u>For others factors:</u><br>Not exposed: almost never, rarely                                  |

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Table 1 (continued)

| Factors                                                   | Job exposure matrix or database                                                | Construction   | Occupation nomenclatures | Industry activities nomenclatures | Metrics             | Temporal axis/Gender-specific | Exposure parameter used in analyses                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------------------|--------------------------------------------------------------------------------|----------------|--------------------------|-----------------------------------|---------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                           |                                                                                |                |                          |                                   |                     |                               | Exposed: often, almost always                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>5) Organizational factors</b>                          |                                                                                |                |                          |                                   |                     |                               |                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Night work                                                | Matgéné – night work France (Houot et al., 2022)                               | Questionnaires | PCS-1982<br>PCS-2003     | NAF-1993<br>NAF-2003<br>NAF-2008  | Probability         | Yes<br>1993–2017/<br>Yes      | Not exposed: no or 0 %<br>Exposed: yes (ELFE data <sup>a</sup> ) or >50 % (JEM data when missing data)<br><u>For intensity of physical efforts:</u><br>Not exposed: no physical effort, extremely light, very light, light<br>Exposed: slightly difficult, challenging, very difficult, extremely difficult, exhausting<br><u>For others factors:</u><br>Not exposed: almost never, rarely<br>Exposed: often, almost always |
| Interruption of tasks<br>Working outdoors                 | JEM Constances France (Evanoff et al., 2019)                                   | Questionnaires | PCS-2003                 | –                                 | Bias-corrected mean | No/No                         |                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>6) Psychosocial factors</b>                            |                                                                                |                |                          |                                   |                     |                               |                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Low decision authority<br>High job demands<br>High strain | Swedish psychosocial JEM Sweden (Almroth et al., 2021; Solovieva et al., 2022) | Questionnaires | SSYK-1996                | –                                 | Intensity           | No/Yes                        | <u>For decision demands:</u><br>Not exposed: low, medium, medium low<br>Exposed: high, medium high<br><u>For job strain:</u><br>Not exposed: low, passive<br>Exposed: high, active                                                                                                                                                                                                                                          |

<sup>a</sup> Chlorinated solvents: at least one of the following: trichloroethylene, tetrachloroethylene, dichloromethane, tetrachloromethane, trichloromethane.

<sup>b</sup> Oxygenated solvents: at least one of the following: alcohols, ethylene glycol, ketones/esters, diethyl ether, tetrahydrofuran.

<sup>c</sup> Fuels and petroleum-based solvents: at least one of the following: benzene, special petroleum products and other aliphatic petroleum-based solvents, gasoline, white spirit and aliphatic petroleum-based solvents, kerosene/fuel oils/diesel).

<sup>d</sup> Endocrine disruptors: at least one of the following: polycyclic aromatic hydrocarbons, polychlorinated organic compounds, pesticides, phthalates, organic solvents, bisphenol A, alkylphenolic compounds, brominated flame retardants, metals (arsenic, cadmium, copper, lead, and mercury), other molecules (benzophenones, parabens, and siloxanes).

<sup>e</sup> These occupational exposures were not studied because fewer than five women were exposed.

<sup>f</sup> Some biological factors were evaluated with database.

<sup>g</sup> For night work, exposure data were collected from ELFE questionnaires. Missing data ( $n = 3194$ ) were replaced with data from the JEM.

in Appendix E: the included mothers mostly had a university level of education (69.2 % vs xxx% for non-included), less tobacco consumption (17.9 % vs 25.5 %), less frequently hospitalized (14.6 % vs 21.1 %) and with less cases of SGA (8.6 % vs 16.7 % for non-included). Others characteristics were similar among groups. The mean age of these women at inclusion was 31.1 years (SD = 4.7 years). More than two thirds had a university degree ( $n = 8863$ ; 69.2 %). Before pregnancy, most of the women had a normal BMI ( $n = 8604$ ; 67.9 %). During pregnancy, just under 20 % of mothers smoked ( $n = 2279$ ; 17.9 %) or consumed alcohol ( $n = 2077$ ; 18.7 %). The mean duration of work during pregnancy was 27 weeks (SD = 7.9 weeks), with only 10.2 % ( $n = 1283$ ) of mothers stopping work in the first trimester, 32.5 % ( $n = 4074$ ) stopping work in the second trimester and 57.3 % ( $n = 7179$ ) in the third trimester. Mean gestational age at delivery was 39.3 weeks (SD = 1.4 weeks). The mean BW of the neonates was 3338.8 g (SD = 471.3 g), and 8.6 % of the neonates were SGA. The mean HC of the neonates was 34.4 cm (SD = 1.4 cm) (Table 2).

### 3.2. Occupational characteristics during pregnancy

During pregnancy, the majority of mothers worked in professional and technical (41.2 %), followed by clerical (23.9 %), service (16.6 %), sales (11.1 %), managerial (3.6 %), production (3.1 %), and agricultural (0.8 %) jobs (Appendix F).

During pregnancy, the most common chemical exposures among mothers were oxygenated solvents (20.3 %) and detergents (17.7 %). Regarding physical factors, 10 % of women were exposed to low-frequency magnetic fields. Among biological factors, airborne microbes affected one-third of the population (33.3 %), while exposure to cytomegalovirus/parvovirus B19 (17.3 %) and hepatitis B/C (15.4 %) was also noted. The most prevalent strength-related factor was the intensity of physical efforts (47.5 %). Postural factors included frequent use of a computer screen or control panel (66.6 %) and prolonged standing (58.8 %). In terms of organizational factors, 57.8 % of mother's experienced task interruptions at work, while fewer than 10 % were exposed to night shifts. Finally, among psychosocial factors, 51.8 % of women faced high strain, 40 % had highly demanding jobs, and 40.1 % had limited decision-making authority at work (Table 3). The

**Table 2**Characteristics of the population. ELFE study, France,  $n = 12,851$ .

|                                           | All $N = 12,851$ |                         | SGA $N = 1084$ |                         | Not SGA $N = 11,480$ |                         |
|-------------------------------------------|------------------|-------------------------|----------------|-------------------------|----------------------|-------------------------|
|                                           | $n$ (%)          | Mean (SD <sup>a</sup> ) | $n$ (%)        | Mean (SD <sup>a</sup> ) | $n$ (%)              | Mean (SD <sup>a</sup> ) |
| <b>Socioeconomic data</b>                 |                  |                         |                |                         |                      |                         |
| Maternal age (years)                      |                  | 31.1 (4.7)              |                | 31.0 (4.9)              |                      | 31.1 (4.7)              |
| Unknown                                   | 52               |                         | 5              |                         | 26                   |                         |
| Mother's nationality                      |                  |                         |                |                         |                      |                         |
| French                                    | 12,161 (95.5)    |                         | 1025 (95.4)    |                         | 10,897 (95.5)        |                         |
| Other nationality                         | 571 (4.5)        |                         | 48 (4.5)       |                         | 505 (4.4)            |                         |
| Stateless                                 | 4 (0.0)          |                         | 1 (0.1)        |                         | 3 (0.0)              |                         |
| Unknown                                   | 115              |                         | 10             |                         | 75                   |                         |
| Maternal education level <sup>b</sup>     |                  |                         |                |                         |                      |                         |
| Low                                       | 249 (1.9)        |                         | 38 (3.5)       |                         | 210 (1.8)            |                         |
| High-school                               | 3692 (28.8)      |                         | 368 (34.1)     |                         | 3237 (28.2)          |                         |
| University                                | 8863 (69.2)      |                         | 673 (62.4)     |                         | 8012 (69.9)          |                         |
| Unknown                                   | 47               |                         | 5              |                         | 21                   |                         |
| In a relationship                         | 12,287 (96.5)    |                         | 1011 (94.0)    |                         | 11,028 (96.7)        |                         |
| Unknown                                   | 120              |                         | 9              |                         | 81                   |                         |
| Marital status                            |                  |                         |                |                         |                      |                         |
| Single                                    | 4474 (35.6)      |                         | 456 (43.1)     |                         | 3931 (34.9)          |                         |
| Cohabiting                                | 2221 (17.7)      |                         | 170 (16.1)     |                         | 2015 (17.9)          |                         |
| Married                                   | 5733 (45.7)      |                         | 420 (39.7)     |                         | 5186 (46.1)          |                         |
| Divorced                                  | 116 (0.9)        |                         | 12 (1.1)       |                         | 104 (0.9)            |                         |
| Widow                                     | 13 (0.1)         |                         | 0 (0.0)        |                         | 12 (0.1)             |                         |
| Unknown                                   | 294              |                         | 26             |                         | 232                  |                         |
| Monthly household income (Euros)          |                  |                         |                |                         |                      |                         |
| <2500                                     | 2289 (18.9)      |                         | 241 (23.5)     |                         | 1990 (18.4)          |                         |
| 2500–4000                                 | 6713 (55.5)      |                         | 568 (55.4)     |                         | 6013 (55.7)          |                         |
| >4000                                     | 3095 (25.6)      |                         | 217 (21.2)     |                         | 2792 (25.9)          |                         |
| Unknown                                   | 754              |                         | 58             |                         | 685                  |                         |
| <b>Before pregnancy</b>                   |                  |                         |                |                         |                      |                         |
| Body mass index (kg/m <sup>2</sup> )      |                  |                         |                |                         |                      |                         |
| <18.5                                     | 932 (7.4)        |                         | 130 (12.1)     |                         | 778 (6.9)            |                         |
| 18.5–24.9                                 | 8573 (67.6)      |                         | 723 (67.4)     |                         | 7685 (67.7)          |                         |
| 25.0–29.9                                 | 2116 (16.7)      |                         | 148 (13.8)     |                         | 1934 (17.0)          |                         |
| ≥30                                       | 1052 (8.3)       |                         | 71 (6.6)       |                         | 955 (8.4)            |                         |
| Unknown                                   | 178              |                         | 12             |                         | 128                  |                         |
| Diabetes (type 1 or 2)                    | 115 (0.9)        |                         | 14 (1.3)       |                         | 100 (0.9)            |                         |
| Unknown                                   | 371              |                         | 24             |                         | 237                  |                         |
| Chronic high blood pressure               | 284 (2.3)        |                         | 35 (3.3)       |                         | 243 (2.1)            |                         |
| Unknown                                   | 268              |                         | 18             |                         | 142                  |                         |
| <b>During pregnancy</b>                   |                  |                         |                |                         |                      |                         |
| Parity                                    |                  |                         |                |                         |                      |                         |
| Primiparous                               | 6153 (48.3)      |                         | 631 (58.9)     |                         | 5393 (47.3)          |                         |
| Multiparous                               | 6587 (51.7)      |                         | 440 (41.1)     |                         | 6016 (52.7)          |                         |
| Unknown                                   | 111              |                         | 13             |                         | 71                   |                         |
| Number of deliveries                      |                  | 1.4 (0.7)               |                | 1.4 (0.8)               |                      | 1.4 (0.7)               |
| Unknown                                   | 6857             |                         | 674            |                         | 5975                 |                         |
| Hypertensive disorders                    | 405 (3.2)        |                         | 91 (8.6)       |                         | 310 (2.8)            |                         |
| Unknown                                   | 360              |                         | 22             |                         | 212                  |                         |
| Preeclampsia                              | 149 (1.2)        |                         | 51 (4.8)       |                         | 96 (0.9)             |                         |
| Unknown                                   | 360              |                         | 22             |                         | 212                  |                         |
| Smoking                                   | 2279 (17.9)      |                         | 302 (28.1)     |                         | 1936 (17.0)          |                         |
| Unknown                                   | 136              |                         | 10             |                         | 97                   |                         |
| Alcohol consumption                       |                  |                         |                |                         |                      |                         |
| No                                        | 9024 (81.3)      |                         | 753 (81.6)     |                         | 8104 (81.4)          |                         |
| <1 glass per month                        | 1637 (14.7)      |                         | 131 (14.2)     |                         | 1464 (14.7)          |                         |
| ≥1 glass per month                        | 440 (4.0)        |                         | 39 (4.2)       |                         | 390 (3.9)            |                         |
| Unknown                                   | 1750             |                         | 161            |                         | 1522                 |                         |
| Time at which stopped work                |                  |                         |                |                         |                      |                         |
| 1st trimester                             | 1283 (10.2)      |                         | 151 (14.1)     |                         | 1116 (9.9)           |                         |
| 2nd trimester                             | 4074 (32.5)      |                         | 397 (37.2)     |                         | 3627 (32.1)          |                         |
| 3rd trimester                             | 7179 (57.3)      |                         | 520 (48.7)     |                         | 6565 (58.1)          |                         |
| Unknown                                   | 315              |                         | 16             |                         | 172                  |                         |
| Duration of work during pregnancy (weeks) |                  | 27.4 (7.9)              |                | 25.9 (8.5)              |                      | 27.5 (7.8)              |
| Unknown                                   | 376              |                         | 23             |                         | 238                  |                         |
| Hospitalization                           | 1857 (14.6)      |                         | 304 (28.4)     |                         | 1507 (13.2)          |                         |
| Unknown                                   | 130              |                         | 12             |                         | 86                   |                         |
| Workplace adjustment <sup>d</sup>         | 1663 (15.1)      |                         | 141 (15.3)     |                         | 1489 (15.1)          |                         |
| Unknown                                   | 1828             |                         | 160            |                         | 1624                 |                         |

**Childbirth**

(continued on next page)

Table 2 (continued)

|                                                 | All N = 12,851 |                         | SGA N = 1084 |                         | Not SGA N = 11,480 |                         |
|-------------------------------------------------|----------------|-------------------------|--------------|-------------------------|--------------------|-------------------------|
|                                                 | n (%)          | Mean (SD <sup>a</sup> ) | n (%)        | Mean (SD <sup>a</sup> ) | n (%)              | Mean (SD <sup>a</sup> ) |
| Gestational age (weeks of gestation)            |                | 39.3 (1.4)              |              | 37.5 (2.0)              |                    | 39.5 (1.2)              |
| Unknown                                         | 200            |                         | 10           |                         | 81                 |                         |
| Mode of delivery                                |                |                         |              |                         |                    |                         |
| Cesarean                                        | 2141 (17.1)    |                         | 279 (26.2)   |                         | 1835 (16.3)        |                         |
| Vaginal delivery                                | 10,376 (82.9)  |                         | 784 (73.8)   |                         | 9449 (83.7)        |                         |
| Unknown                                         | 334            |                         | 21           |                         | 196                |                         |
| Infant's sex                                    |                |                         |              |                         |                    |                         |
| Female                                          | 6283 (49.3)    |                         | 584 (54.0)   |                         | 5573 (48.6)        |                         |
| Male                                            | 6458 (50.7)    |                         | 497 (46.0)   |                         | 5901 (51.4)        |                         |
| Unknown                                         | 110            |                         | 3            |                         | 6                  |                         |
| Birthweight (in grams)                          |                | 3338.8 (471.3)          |              | 2531.8 (356.1)          |                    | 3415.2 (402.0)          |
| Unknown                                         | 272            |                         | 4            |                         | 20                 |                         |
| Small for gestational age <sup>c</sup>          | 1084 (8.6)     |                         | –            |                         | –                  |                         |
| Severely small for gestational age <sup>c</sup> | 407 (3.2)      |                         | –            |                         | –                  |                         |
| Unknown                                         | 287            |                         | –            |                         | –                  |                         |
| Head circumference (in centimeters)             |                | 34.4 (1.4)              |              | 32.6 (1.2)              |                    | 34.6 (1.3)              |
| Unknown                                         | 1439           |                         | 171          |                         | 985                |                         |

<sup>a</sup> SD: standard deviation.

<sup>b</sup> Low = never attended school, or attended only primary and middle school; High = educated to level certificate of vocational aptitude, professional qualifications, high-school diploma; University = attended a higher education establishment.

<sup>c</sup> SGA defined as a BW below the 10th percentile for gestational age and sex according to WHO curves. Severely SGA = BW below the 3rd percentile for gestational age and sex.

<sup>d</sup> Workplace adjustment, carried out by the occupational physician, refers to modifications or accommodations made to a job, work environment, or way of working to support an employee's health, safety, or productivity — particularly in cases of disability, illness, or specific needs.

correlations between these occupational exposures are detailed in Appendix G.

### 3.3. Multiple occupational exposures during pregnancy and their effects on intrauterine growth

The exposure ranking step, in the EWAS (Appendix H1), LASSO (Appendix H2) and random forest (Appendix H3) approaches, identified exposure to endocrine disrupters, high strain, kneeling or squatting, a highly demanding job and the intensity of physical effort as the most important occupational exposures for SGA (Table 4, Appendix H4). The final model, including these five variables and an interaction between endocrine disrupter and high strain, job demands and intensity of physical effort (Appendix H5), revealed no significant associations (Fig. 1A). However, there was a non-significant increase in the risk of the infant being SGA associated with occupational exposure to high strain (OR = 1.15, 95 % CI = 0.94 to 1.40) (Fig. 1A). The results of analyses considering only the top five most important exposures selected by EWAS, LASSO or random forest separately are presented in Appendix H6.

The exposure ranking step, in the EWAS (Appendix I1), LASSO (Appendix I2) and random forest (Appendix I3) approaches revealed that leaning forward or sideways, using a computer screen or control panel, ultrafine particles, the intensity of physical effort, airborne germs and repetitive actions were the most important occupational exposures related to BW (Table 5, Appendix I4). The final model, including these variables and interactions between leaning forward or sideways and airborne germs, ultrafine particles and intensity of physical effort (Appendix I5), indicated that leaning forward or sideways during work was positively associated with BW ( $\beta = 38$ , 95 % CI = 4.6 to 71), and using a computer screen or control panel was negatively associated with BW ( $\beta = -22$ , 95 % CI = -44 to -0.57). A significant interaction between leaning forward or sideways and exposure to airborne germs was also detected ( $p = 0.03$ ) (Fig. 1B). Among women not exposed to airborne germs, leaning forward or sideways increased BW significantly, by 38 g (95 % CI = 4.6 to 71). By contrast, no such association was detected in women exposed to airborne germs (Fig. 1D). We found that 36.1 % of the women in occupations involving leaning forward or sideways without exposure to airborne microbes were cleaners and helpers, 10 % were teachers and 9.5 % were social workers. Women

whose jobs involved both leaning forward or sideways and exposure to airborne germs were healthcare professionals in 45.5 % of cases (27.3 % were nurses, midwives, medical or radiology technicians and 18.2 % were nursing assistants) and preschool and primary school teachers in 22.9 % of cases. The results of the analyses considering only the results of the EWAS, LASSO or random forest approaches are presented separately in Appendix I6.

The exposure ranking step, in the EWAS (Appendix J1), LASSO (Appendix J2) and random forest (Appendix J3) analyses for HC revealed that repetitive actions, oxygenated solvents, kneeling or squatting, airborne germs, and working outdoors were the most important occupational exposures related to this outcome (Table 6, Appendix J4). The final model included these five variables and interactions between oxygenated solvents and repetitive actions, oxygenated solvents and kneeling, and between oxygenated solvents and airborne germs (Appendix J5). In this final model, repetitive actions ( $\beta = -0.09$ , 95 % CI = -0.16 to -0.03), exposure to oxygenated solvents ( $\beta = -0.28$ , 95 % CI = -0.42 to -0.14) and working outdoors ( $\beta = -0.13$ , 95 % CI = -0.22 to -0.03) were significantly associated with HC and there was a significant interaction between exposures to oxygenated solvents and airborne germs ( $p = 0.04$ ) (Fig. 1C). Exposure to oxygenated solvents was associated with a decrease of 0.13 (95 % CI = -0.26 to 0.00) cm and 0.28 (95 % CI = -0.42 to -0.14) cm in the HC of neonates born to women exposed and unexposed, respectively, to airborne germs (Fig. 1E). The women exposed to oxygenated solvents but not to airborne germs were employed as cleaners (26.9 %), laboratory technicians (10.6 %) and nurses (10.2 %). In terms of industrial activity codes, 10.8 % worked as medical auxiliaries and 10.1 % were involved in cleaning activities. The women exposed to both oxygenated solvents and airborne microbes included 27.5 % nurses and 25.1 % nursing assistants. Most of the women (53.5 %) worked in hospitals according to the industrial activities' nomenclature. The results of the separate analyses of exposures selected by EWAS, LASSO or random forest are presented in Appendix J6.

### 3.4. Sensitivity analyses

Sensitivity analyses on women who continued work until the third trimester of pregnancy are presented in Appendix H7 for SGA, Appendix I7 for BW, and Appendix J7 for HC. The results for SGA and HC were

**Table 3**  
Description of the occupational exposure of women during pregnancy. ELFE study, France, *n* = 12,851.

|                                              | Not exposed <i>n</i><br>(%) | Exposed <i>n</i><br>(%) | Missing |
|----------------------------------------------|-----------------------------|-------------------------|---------|
| <b>Chemical factors</b>                      |                             |                         |         |
| Solvents                                     |                             |                         |         |
| Chlorinated                                  | 12,453 (99.9)               | 10 (0.1) <sup>a</sup>   | 388     |
| Oxygenated                                   | 9881 (79.7)                 | 2520 (20.3)             | 450     |
| Petroleum                                    | 12,351 (99.7)               | 37 (0.3) <sup>b</sup>   | 463     |
| Detergents                                   | 10,226 (82.3)               | 2193 (17.7)             | 432     |
| Pesticides                                   | 10,310 (99.2)               | 80 (0.8)                | 2461    |
| Heavy metals                                 |                             |                         |         |
| Arsenic                                      | 12,640<br>(100.0)           | 0 <sup>a</sup>          | 211     |
| Cadmium                                      | 12,620<br>(100.0)           | 0 <sup>a</sup>          | 231     |
| Chromium                                     | 12,637<br>(100.0)           | 0 <sup>a</sup>          | 214     |
| Iron                                         | 12,636<br>(100.0)           | 2 (0.0) <sup>a</sup>    | 213     |
| Lead                                         | 12,606<br>(100.0)           | 0 <sup>a</sup>          | 245     |
| Nickel                                       | 12,636<br>(100.0)           | 0 <sup>a</sup>          | 215     |
| Nanoparticles                                |                             |                         |         |
| Ultrafine particles                          | 11,137 (94.2)               | 689 (5.8)               | 1025    |
| Welding fumes                                | 12,636<br>(100.0)           | 2 (0.0) <sup>a</sup>    | 213     |
| Polycyclic aromatic hydrocarbons             | 12,637<br>(100.0)           | 0 <sup>a</sup>          | 214     |
| Benzo(a)pyrene                               | 12,644<br>(100.0)           | 0 <sup>a</sup>          | 214     |
| Carbon monoxide                              | 12,270<br>(100.0)           | 0 <sup>a</sup>          | 578     |
| Endocrine disruptors and other chemicals     | 11,966 (95.6)               | 549 (4.4)               | 336     |
| <b>Physical factors</b>                      |                             |                         |         |
| Ionizing radiation                           | 10,059 (82.8)               | 2083 (17.2)             | 709     |
| Low-frequency magnetic fields                | 10,658 (89.3)               | 1277 (10.7)             | 916     |
| Non-thermal intermediate frequency           |                             | 0 <sup>a</sup>          | 1368    |
| Radiofrequency (E field)                     |                             |                         |         |
| Radiofrequency (E field)                     |                             | 23 (0.2) <sup>b</sup>   | 1368    |
| Radiofrequency (H field)                     |                             | 8 (0.1) <sup>a</sup>    | 1368    |
| Thermal intermediate frequency (E field)     |                             | 0 <sup>a</sup>          | 1368    |
| Thermal intermediate frequency (H field)     |                             | 0 <sup>a</sup>          | 1368    |
| Ultraviolet                                  |                             | 89 (0.7) <sup>b</sup>   | 664     |
| <b>Biological factors</b>                    |                             |                         |         |
| Airborne germs                               | 8062 (66.7)                 | 4019 (33.3)             | 770     |
| Cytomegalovirus, parvovirus B19              | 10,280 (82.7)               | 2145 (17.3)             | 426     |
| Hepatitis A, E                               | 11,512 (92.6)               | 919 (7.4)               | 420     |
| Hepatitis B, C, human immunodeficiency virus | 10,517 (84.6)               | 1914 (15.4)             | 420     |
| <b>Strenuous factors</b>                     |                             |                         |         |
| Strength                                     |                             |                         |         |
| Intensity of physical effort                 | 6316 (52.5)                 | 5716 (47.5)             | 819     |
| Carrying loads of 10–25 kg                   | 11,204 (92.6)               | 897 (7.4)               | 750     |
| Handling loads >4 kg                         | 9827 (81.6)                 | 2222 (18.4)             | 802     |
| Posture                                      |                             |                         |         |
| Arms raised above the shoulders              | 10,624 (86.7)               | 1631 (13.3)             | 596     |
| Standing                                     | 4996 (41.5)                 | 7037 (58.5)             | 818     |
| Kneeling or squatting                        | 9098 (74.9)                 | 3054 (25.1)             | 699     |
| Leaning forward or sideways                  | 8420 (68.7)                 | 3834 (31.3)             | 597     |
| Repetitive actions                           | 7832 (64.2)                 | 4375 (35.8)             | 644     |
| Vibration                                    |                             |                         |         |
| Using vibrating tools                        | 12,372 (99.2)               | 105 (0.8)               | 374     |
| Driving construction machinery               | 12,462 (98.8)               | 150 (1.2)               | 239     |
| Driving a vehicle                            | 11,388 (93.2)               | 828 (6.8)               | 635     |
| Using a computer screen or control panel     | 4049 (33.4)                 | 8073 (66.6)             | 729     |
| <b>Organizational factors</b>                |                             |                         |         |
| Night work                                   | 10,803 (92.5)               | 876 (7.5)               | 1172    |
| Interruption of tasks                        | 5088 (42.2)                 | 6979 (57.8)             | 784     |
| Working outdoors                             | 11,195 (92.4)               | 923 (7.6)               | 733     |
| <b>Psychosocial factors</b>                  |                             |                         |         |

|                                        | Not exposed <i>n</i><br>(%) | Exposed <i>n</i><br>(%) | Missing |
|----------------------------------------|-----------------------------|-------------------------|---------|
| Low level of decision-making authority | 6951 (59.9)                 | 4651 (40.1)             | 1249    |
| Highly demanding job                   | 6962 (60.0)                 | 4642 (40.0)             | 1247    |
| High strain                            | 5596 (48.2)                 | 6008 (51.8)             | 1247    |

<sup>a</sup> These variables have been deleted from the final model (*n* exposed <10).  
<sup>b</sup> These variables have been also deleted from the final model (*n* exposed for SGA <10).

**Table 4**  
Ranking of occupational exposures for SGA across different approaches (EWAS, LASSO, random forest), with the median rank for each occupational exposure. ELFE study, France, *n* = 12,851.

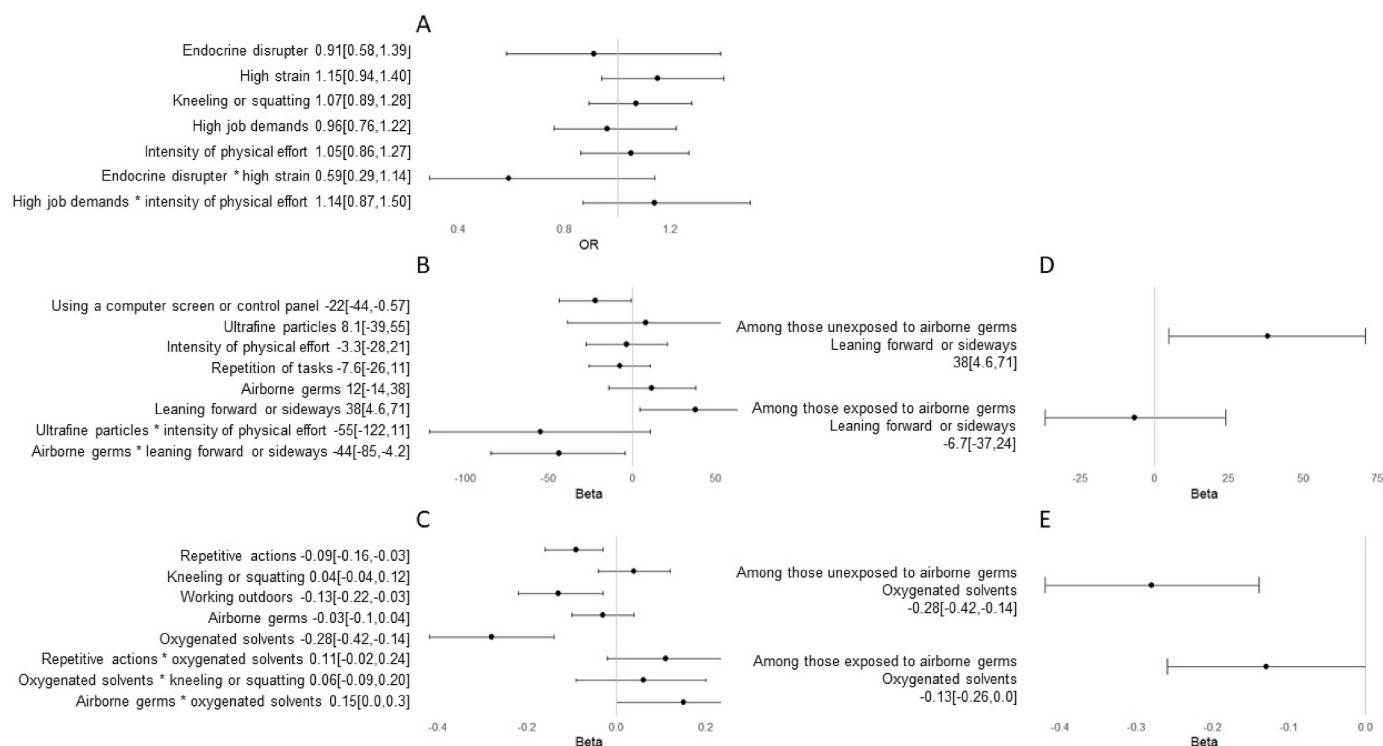
|                                          | EWAS | LASSO | Random forest | Median <sup>a</sup> |
|------------------------------------------|------|-------|---------------|---------------------|
| Endocrine disrupter                      | 1    | 2     | 24            | 2                   |
| High strain                              | 3    | 14    | 2             | 3                   |
| Kneeling or squatting                    | 4    | 9     | 4             | 4                   |
| Highly demanding job                     | 1    | 18    | 5             | 5                   |
| Intensity of physical effort             | 9    | 6     | 6             | 6                   |
| Handling of loads >4 kg                  | 7    | 16    | 7             | 7                   |
| Working outdoors                         | 6    | 8     | 21            | 8                   |
| Hepatitis B, C, HIV                      | 4    | 23    | 9             | 9                   |
| Repetitive actions                       | 12   | 5     | 10            | 10                  |
| Standing                                 | 19   | 10    | 8             | 10                  |
| Interruption of tasks                    | 11   | 4     | 15            | 11                  |
| Ionizing radiation                       | 7    | 26    | 12            | 12                  |
| Cytomegalovirus, parvovirus B19          | 12   | 27    | 11            | 12                  |
| Airborne germs                           | 28   | 7     | 13            | 13                  |
| Oxygenated solvents                      | 14   | 1     | 14            | 14                  |
| Using a computer screen or control panel | 16   | 22    | 3             | 16                  |
| Hepatitis A, E                           | 9    | 24    | 16            | 16                  |
| Leaning forward or sideways              | 17   | 17    | 1             | 17                  |
| Carrying loads of 10–25 kg               | 22   | 15    | 18            | 18                  |
| Driving a vehicle                        | 18   | 11    | 22            | 18                  |
| Raising arms above the shoulders         | 26   | 12    | 19            | 19                  |
| Detergents                               | 19   | 28    | 20            | 20                  |
| Night work                               | 15   | 21    | 23            | 21                  |
| Low decision authority                   | 21   | 25    | 17            | 21                  |
| Driving construction machinery           | 22   | 13    | 28            | 22                  |
| Pesticides                               | 24   | 19    | 27            | 24                  |
| Ultrafine particles                      | 25   | 3     | 26            | 25                  |
| Low-frequency magnetic fields            | 27   | 29    | 25            | 27                  |
| Using vibrating tools                    | 29   | 20    | 29            | 29                  |

<sup>a</sup> The rankings are sorted by median overall rank across approaches.

similar. For BW, using a computer screen or control panel was going in the same direction, but this result was not significant; and leaning forward or sideways was going in the opposite direction.

4. Discussion

We used data-driven approaches based on three independent statistical methods to identify the most important occupational exposures for the outcomes considered. In the resulting final regression models incorporating the top five exposures and relevant interaction terms, we identified several significant associations between occupational exposures and birth outcomes. For BW, leaning forward or sideways and using a computer screen or a control panel were identified as relevant exposures and there was a significant interaction between leaning forward or sideways and exposure to airborne germs. Repetitive actions, exposure to oxygenated solvents and working outdoors were associated with HC, and there was an interaction between oxygenated solvents and exposure to airborne germs. No significant associations with SGA were identified. These findings were confirmed for women who continued to work into the third trimester of pregnancy. To the best of our



**Fig. 1.** Relationship between the five most important occupational exposure variables and SGA (A), BW (B), and HC (C), with significant interactions shown. Stratification for exposure to airborne microbes for BW (D) and HC (E). For SGA, analyses were adjusted for educational level, BMI, tobacco consumption, and alcohol consumption; For BW and HC, analyses were adjusted for educational level, BMI, tobacco consumption, alcohol consumption, gestational age, and the sex of the infant. ELFE study, France.

**Table 5**

Ranking of occupational exposures for BW across different approaches (EWAS, LASSO, random forest), with the median rank for each occupational exposure. ELFE study, France,  $n = 12,851$ .

|                                          | EWAS | LASSO | Random forest | Median <sup>a</sup> |
|------------------------------------------|------|-------|---------------|---------------------|
| Leaning forward or sideways              | 1    | 2     | 3             | 2                   |
| Using a computer screen or control panel | 1    | 11    | 2             | 2                   |
| Ultrafine particles                      | 3    | 3     | 26            | 3                   |
| Intensity of physical effort             | 4    | 9     | 1             | 4                   |
| Airborne germs                           | 6    | 6     | 9             | 6                   |
| Repetitive actions                       | 28   | 4     | 6             | 6                   |
| Standing                                 | 7    | 14    | 5             | 7                   |
| Working outdoors                         | 4    | 8     | 21            | 8                   |
| Oxygenated solvents                      | 18   | 1     | 10            | 10                  |
| Kneeling or squatting                    | 10   | 17    | 4             | 10                  |
| Interruption of tasks                    | 24   | 7     | 11            | 11                  |
| Cytomegalovirus, parvovirus B19          | 12   | 27    | 12            | 12                  |
| Endocrine disruptors                     | 13   | 5     | 22            | 13                  |
| Driving a vehicle                        | 8    | 13    | 24            | 13                  |
| Handling of loads >4 kg                  | 8    | 15    | 14            | 14                  |
| High strain                              | 16   | 16    | 7             | 16                  |
| Driving construction machinery           | 17   | 10    | 28            | 17                  |
| Hepatitis B, C, HIV                      | 15   | 28    | 17            | 17                  |
| Carrying loads 10–25 kg                  | 21   | 12    | 19            | 19                  |
| Raising arms above the shoulders         | 20   | 19    | 15            | 19                  |
| Detergents                               | 23   | 20    | 13            | 20                  |
| Hepatitis A, E                           | 10   | 24    | 20            | 20                  |
| Pesticides                               | 19   | 21    | 27            | 21                  |
| Low decision authority                   | 22   | 23    | 18            | 22                  |
| Low-frequency magnetic fields            | 14   | 22    | 23            | 22                  |
| Using vibrating tools                    | 24   | 18    | 29            | 24                  |
| High job demands                         | 27   | 25    | 8             | 25                  |
| Night work                               | 26   | 26    | 25            | 26                  |
| Ionizing radiation                       | 29   | 29    | 16            | 29                  |

<sup>a</sup> The rankings are sorted by the median overall rank across approaches.

**Table 6**

Ranking of occupational exposures for HC across different approaches (EWAS, LASSO, random forest), with the median rank for each occupational exposure. ELFE study, France,  $n = 12,851$ .

|                                          | EWAS | LASSO | Random forest | Median <sup>a</sup> |
|------------------------------------------|------|-------|---------------|---------------------|
| Repetitive actions                       | 2    | 2     | 12            | 2                   |
| Oxygenated solvents                      | 4    | 1     | 8             | 4                   |
| Kneeling or squatting                    | 12   | 6     | 4             | 6                   |
| Airborne germs                           | 12   | 5     | 6             | 6                   |
| Working outdoors                         | 1    | 7     | 22            | 7                   |
| Standing                                 | 11   | 9     | 2             | 9                   |
| High strain                              | 5    | 21    | 9             | 9                   |
| Intensity of physical effort             | 19   | 10    | 3             | 10                  |
| Endocrine disruptors                     | 10   | 4     | 21            | 10                  |
| Leaning forward or sideways              | 28   | 11    | 1             | 11                  |
| Handling loads >4 kg                     | 22   | 12    | 10            | 12                  |
| Hepatitis B, C, HIV                      | 6    | 26    | 13            | 13                  |
| Raising arms above the shoulders         | 7    | 23    | 14            | 14                  |
| Ultrafine particles                      | 14   | 3     | 26            | 14                  |
| Low decision authority                   | 8    | 28    | 16            | 16                  |
| Pesticides                               | 15   | 16    | 28            | 16                  |
| Using a computer screen or control panel | 21   | 17    | 7             | 17                  |
| High job demands                         | 17   | 22    | 11            | 17                  |
| Interruption of tasks                    | 26   | 8     | 17            | 17                  |
| Driving a vehicle                        | 18   | 14    | 24            | 18                  |
| Carrying loads 10–25 kg                  | 20   | 15    | 19            | 19                  |
| Low-frequency magnetic fields            | 16   | 19    | 23            | 19                  |
| Hepatitis A, E                           | 9    | 27    | 20            | 20                  |
| Night work                               | 3    | 20    | 25            | 20                  |
| Using vibrating tools                    | 22   | 18    | 27            | 22                  |
| Cytomegalovirus, parvovirus B19          | 24   | 25    | 5             | 24                  |
| Ionizing radiation                       | 28   | 24    | 18            | 24                  |
| Detergents                               | 25   | 29    | 15            | 25                  |
| Driving construction machinery           | 27   | 13    | 29            | 27                  |

<sup>a</sup> The rankings are sorted by the median overall rank across approaches.

knowledge, this is the first study to assess the contributions to intrauterine growth, using data driven approaches, of a large set of occupational exposures during pregnancy. These results are consistent with those of a previous analysis of the same ELFE cohort, which used a clustering approach to identify four distinct maternal occupational exposome profiles (Tartaglia et al., 2024). One profile, characterized by “postural constraints and psychosocial factors” was found to be associated with a higher risk of SGA and HC, among women who continued to work into the third trimester of pregnancy. These findings reinforce the role of postural and psychosocial constraints on intrauterine growth outcomes.

In the exposure ranking step, the ranks assigned to each type of occupational exposure differed between the three methods used. However, in most cases, the final top five occupational exposures based in the median were ranked within the top five for at least two of the three methods (EWAS, LASSO, random forest). Combining several different methods increases the likelihood of capturing the most important occupational exposures and their relationships to intrauterine growth. However, the results of the analyses of final models based on the results of a single method (EWAS, LASSO or RF) differed from those of the final model based on the median score (combining EWAS, LASSO and random forest results). This can be explained by the fact that EWAS likely focuses on univariate associations and may highlight exposures with strong marginal effects, LASSO performs variable selection with penalization, favoring factors with more consistent effects when accounting for others, and random forest, being a tree-based ensemble method, can minimize variables that are less important in complex, nonlinear interactions. The combination of different methods may have increased clarity and performance and improved the visualization of the results, while reducing the risks associated with high dimensionality (Ohanyan et al., 2022). We used two of the three methods recommended by Staffoglia et al. (Staffoglia et al., 2017) — variable selection (EWAS, LASSO) and clustering (random forest) — but not the third (dimension reduction). Variable selection is an alternative to dimension reduction and is sufficient to reduce complexity and to decrease the risk of redundancy. The data-driven approach used here allowed an exploratory analysis of a complex dataset of occupational exposures. For the final model, we selected a cut-off of five variables to include, based on consensus among five co-authors (MT, CG, AP, RG, FD). While this threshold provided a manageable number of exposures for interpretation, a different cut-off could have been chosen, which might have led to slightly different results. Finally, single-exposure approaches often identify a larger proportion to significant associations and underestimate effects (Staffoglia et al., 2017).

In our final model, using a computer screen or control panel was associated with a significant decrease in BW. To the best of our knowledge, no previous epidemiological study on this type of occupational exposure has ever before reported an association with BW. Screen work may serve as a proxy for working in a seated position. The postural constraints associated with working in this position during pregnancy may explain the decrease in BW or simply because it is associated with a lower exposure to an important other factor, such as found in musculoskeletal disorders (Mediouni et al., 2015). We also observed a significant interaction between leaning forward or sideways and exposure to airborne germs, resulting in a significant increase in BW by 38 g (95 % CI = 4.6 to 71) exclusively in women who were not exposed to airborne germs but whose occupations involved leaning forward or sideways. Leaning forward or sideways was investigated in one previous study (Bonzini et al., 2009), but no association was found with SGA, BW, or HC, and there are no biological/pathophysiological hypotheses to account for a possible effect of this factor. Most of the women in this category were cleaners and helpers (36.1 %), teachers (10.0 %), and social workers (9.5 %), and many stopped working during the second trimester (46.4 %). By contrast, the women exposed to both leaning and airborne germs (most of whom were healthcare professionals (45.5 %) and preschool and primary school teachers (22.9 %)) most frequently

stopped working during the third trimester (45.1 %). Stopping work earlier or the absence of exposure to airborne germs at work may decrease the cumulative impact of exposures and promote optimal conditions for intrauterine growth.

Several significant associations were observed in our final model for HC. We found that repetitive actions, working outdoors and exposure to oxygenated solvents were all significantly associated with a smaller HC. The effect of repetitive actions may be explained by limiting changes in posture, potentially decreasing venous return and causing muscle tension, particularly in the back, shoulders, and wrists. For women working in awkward postures or exposure to vibrations, concerns have been raised about a potential increase in the risk of intrauterine growth retardation (*Interventions recommandées par I*). In their 2023 review, Rekha et al. found that working outdoors increased the risk of heat-related diseases, with the increase in body temperature of the mother potentially affecting the unborn child (Rekha et al., 2023). In addition, women who work outdoors are more likely to perform physical work, with multiple constraints, such as exposure to high and low temperatures, outdoor air pollution, or pesticides. We also found that occupational exposure to oxygenated solvents was associated with a significantly smaller HC. Animal studies have shown that some solvents can cross the placental barrier (Donald et al., 1991; Elkin et al., 2020; Loch-Carusio et al., 2019) and that several of these solvent may be neurotoxic. In humans, several studies have highlighted the potential impact of these occupational exposures on neurodevelopment, but very few have investigated their impact on HC. Enderle et al. (2023) reported a significant decrease in HC related to these exposures based on the same population study. Interestingly, our study confirmed this result through a data-driven approach with adjustment for the most important other occupational exposures. It also showed that this effect was greater (but in the same direction) in women unexposed to airborne germs. Similarly, in a cluster analysis study, the profile “postural and strength constraints, chemical and biological factors” they identified showed high exposure to oxygenated solvents and airborne germs (Tartaglia et al., 2024). Although not significantly associated with HC in that analysis, this exposure pattern supports our finding that the combination of these factors may play a role in fetal growth. The women exposed to oxygenated solvents but not to airborne germs were cleaners (26.9 %), laboratory technicians (10.6 %), and nurses working as medical auxiliaries (10.2 %). The women exposed to both oxygenated solvents and airborne germs included 27.5 % nurses, and 25.1 % nursing assistants. Medical professionals may be exposed to airborne germs through regular contact with patients. They also use oxygenated solvents, such as certain alcohols used for disinfection.

Finally, no significant association was found with SGA, contrary to published reports of an association between some occupational exposures, such as solvents (Enderle et al., 2023; Ahmed and Jaakkola, 2007), pesticides (Shirangi et al., 2020), ultrafine particles (Manangama et al., 2019, 2020), physical effort (Vrijkotte et al., 2009; Arafa et al., 2007; Hanke and Hausman, 2000), standing (Croteau et al., 2006; Fortier et al., 1995; Cerón-Mireles et al., 1996; Lj et al., 1990), using vibrating tools (Skröder et al., 2021), low level of decision-making authority (Sejbaek et al., 2018), high strain (Vrijkotte et al., 2009; Arafa et al., 2007; Larsen et al., 2013) and SGA. Furthermore, in 2018, Sejbaek et al. reported a multiplicative interaction between lifting and stress, significantly increasing the risk of the neonate being SGA (Sejbaek et al., 2018). These differences may be explained by differences in the characterization of occupational exposures (measurement, questionnaire or JEM), and/or the thresholds used to define exposure. For our analysis, we decided, a priori, to define exposure with a 50 % threshold to increase specificity. However, this increase in specificity is achieved at the cost of a decrease in sensitivity, which may explain, at least partly, why some of the relationships between occupational exposures and intrauterine growth reported in previous studies did not emerge in this analysis.

Our assessment of 47 types of occupational exposure during

pregnancy was based on JEMs or database. However, other factors, such as occupational exposure to noise (Ulin et al., 2024) or heat (Rekha et al., 2023), potentially associated with adverse pregnancy outcomes might also have been of relevance. Internationally recognized JEMs ensure standardized evaluations, despite their limitation of classifying all workers doing the same job in an identical manner (Ge et al., 2018). JEMs based on international data obtained outside of France (endocrine disruptors, FinJEM, Swedish psychosocial JEM, RF-JEM, CANJEM) may have led to the misclassification of some of the exposures assessed, although this effect is probably minimal within high-income countries. Only two gender-specific JEMs (Matg  n   night work and Swedish psychosocial JEM) were used. For biomechanical factors, JEM Constances have shown similar predictivity between gender and non-gender JEM (Wuytack et al., 2024). As most non-gender-specific JEMs are based on male populations, there may have been some misclassification of exposure, potentially causing a bias in exposure estimates. Temporal dimensions were included in some JEMs, to account for changes in work practices and regulations, especially for exposure to chemicals. For biological, strenuous, and psychosocial exposures, temporal stability was assumed. In the variability of JEM validity and the existence of fewer tools for psychosocial and strenuous exposures may also introduce non-differential measurement errors, with a potential impact on the results.

We excluded non-working pregnant women to limit the healthy worker effect, as they are generally in poorer health, at higher risk of adverse pregnancy outcomes, and predominantly exposed to poorly characterized non-occupational environments (Casas et al., 2015).

The strengths of this study include the large number of participants from the French Longitudinal Study of Children, the ELFE study, for whom detailed data are available concerning the occupation of women during pregnancy, including the duration of work during pregnancy, outcomes of interest and confounding factors. A second strength is the details of tasks making it possible for a single expert to code occupations according to international and national occupations (ISCO-1968 and PCS-1994) and industrial activities (CITI-1975 and NAF-2003) nomenclatures. This made it possible to use different JEMs to characterize and analyze a large number of occupational exposures ( $n = 47$ ). A third strength was the combination of different statistical approaches, considering complex multiple exposures and interactions, to find the most consistent associations between exposure and intrauterine growth. This approach complements previous work using unsupervised clustering methods to explore patterns during pregnancy (Tartaglia et al., 2024). While our current analysis prioritized variable selection and interactions, the clustering method provides an alternative yet complementary perspective, emphasizing the real-life co-occurrence of exposures across multiple domains.

However, this study also had several limitations. The first of these limitations was the use of JEMs, as previously discussed. We cannot rule out the possibility that occupational exposures subject to smaller measurement errors may have been more likely to be selected. Moreover, several occupational exposures could not be studied in this study because of the small number of exposed women. Indeed, the cut-off of  $n < 10$  was applied to ensure model stability in this data-driven framework. Some of these occupational exposures were found associated with fetal growth in epidemiological and/or experimental studies, which leads us to consider them in future studies with larger sample size to allow to properly analyze potential harmful exposure with low prevalence. Finally, the application of machine learning methods in the context of the occupational exposome has been limited to date, because most of the available data are qualitative. For example, other statistical methods such as Bayesian kernel machine regression, more appropriate in the mixture studies, can't be applied in this study because of the qualitative nature of exposures variables. The development of robust statistical approaches tailored to the unique characteristics of the occupational exposome, often involving complex and multivariate datasets, will be required to overcome this limitation. Simulated data

would facilitate this process by providing a controlled environment in which to test and validate these methods. By creating realistic scenarios, simulated data enable researchers to identify potential biases, to assess the reliability of analytical tools, and to optimize methodologies before their application to real-world datasets.

## 5. Conclusion

This study highlights the potential effects of certain chemical, biological, and physically strenuous work factors on intrauterine growth, particularly for BW and HC, with significant interactions stressing the importance of considering multiple exposures in this domain of research. The data-driven approach we have used, without a priori hypothesis, for which it seems necessary to better understand the biological and pathophysiological mechanisms that may exist. Confirmation in additional studies is required, but such consolidated results on multiple exposures are important to adapt prevention strategies more effectively for pregnant women.

## CRedit authorship contribution statement

**Marie Tartaglia:** Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Calvin Ge:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Anjoeka Pronk:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Nathalie Costet:** Writing – review & editing, Methodology. **Sabyne Audignon-Durand:** Writing – review & editing, Resources. **Marie-T  lin Houot:** Writing – review & editing, Resources. **Katarina Kjellberg:** Writing – review & editing, Resources. **Maxime Turuban:** Writing – review & editing, Resources. **Nel Roeleveld:** Writing – review & editing, Resources. **Jack Siemiatycki:** Writing – review & editing, Resources. **Camille Carles:** Writing – review & editing, Resources. **Corinne Pilorget:** Writing – review & editing, Resources. **Daniel Falkstedt:** Writing – review & editing, Resources. **Sanni Uuksulainen:** Writing – review & editing, Resources. **Michelle C. Turner:** Writing – review & editing, Resources. **Alexis Descatha:** Writing – review & editing, Resources. **Marie No  lle Dufourg:** Writing – review & editing, Resources. **Fleur Delva:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Ronan Garlant  zec:** Writing – review & editing, Supervision, Methodology, Conceptualization.

## Contributors

This work was supported by the French National Research Agency (Project ANR-17-CE36-0002-01) and within the framework of PIA3 (Investment for the Future), project reference: 17-EURE-0019; the Public Health Doctoral Network from the EHESP; and the French-Dutch Network.

## Competing interests

CP and AP were funded through the Dutch Ministry of Social Affairs and Employment.

AD is editor in chief of Archives des maladies professionnelles et de l'environnement (Elsevier).

## Acknowledgments

The Elfe survey is a joint project between the French Institute for Demographic Studies (INED) and the National Institute of Health and Medical Research (INSERM), in partnership with the French blood transfusion service (Etablissement fran  ais du sang, EFS), Sant   publique France, the National Institute for Statistics and Economic Studies (INSEE), the Direction g  n  rale de la sant   (DGS, part of the Ministry of Health and Social Affairs), the Direction g  n  rale de la pr  vention des risques (DGPR, Ministry for the Environment), the Direction de la

recherche, des études, de l'évaluation et des statistiques (DREES, Ministry of Health and Social Affairs), the Département des études, de la prospective et des statistiques (DEPS, Ministry of Culture), and the Caisse nationale des allocations familiales (CNAF), with the support of the Ministry of Higher Education and Research and the Institut national de la jeunesse et de l'éducation populaire (INJEP). Via the RECONAI platform, it receives a government grant managed by the National Research Agency under the "Investissements d'avenir" programme (ANR-11-EQPX-0038 and ANR-19-COHO-0001).

MCT is funded by a Ramón y Cajal fellowship (RYC-2017-01892) from the Spanish Ministry of Science, Innovation and Universities and co-funded by the European Social Fund. ISGlobal acknowledges support from the grant CEX2023-0001290-S funded by MCIN/AEI/10.13039/501100011033, and support from the Generalitat de Catalunya through the CERCA Program. The conduct of the INTEROCC study was funded by the National Institutes for Health (NIH) (grant no. 1R01CA124759-01). Funding for the OccRF Health Study was provided by ANSES No. EST-2018 RF-35.

We thank Jérôme Lavoué and Elisabeth Cardis for sharing JEM.

We thank Julie Sappa from Alex Edelman & Associates for proof-reading the English version of this article.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijheh.2025.114666>.

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