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Study protocol to explore the social effects of environmental exposure and lifestyle behaviours on pregnancy outcome: an overview of cohort of pregnant women study

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ABSTRACT

Introduction A growing number of international studies have highlighted the adverse consequences of lived experience in the first thousand days of pregnancy and early life on the probability of stillbirth, child mortality, inadequate growth and healthy development during both childhood and adulthood. The lived experience of the fetus inside the womb and at the birth is strongly related to both maternal health during pregnancy and maternal exposure to a set of environmental factors known as 'exposome' characteristics, which include environmental exposure, health behaviours, living conditions, neighbourhood characteristics and socioeconomic profile. The aim of our project is to explore the relationships between exposome characteristics and the health status of pregnant women and their newborns. We are particularly interested in studying the relationships between the social inequality of adverse pregnancy outcomes and (1) short-term exposure to atmospheric pollution (MobiFem project) and (2) pregnancy lifestyle (EnviFem project).

Methods and analysis Ours is a prospective, observational and multisite cohort study of pregnant women, involving one teaching hospital across two sites in the Strasbourg metropolitan area.
The research team at University Hospital of Strasbourg (HUS) Health collects data on outcomes and individual characteristics from pregnancy registries, clinical records data and questionnaires administered via email to study participants. Recruitment began in February 2021 and will be complete by December 2021. Participants are recruited from first trimester antenatal ultrasound examinations (conducted on weekdays across both sites); each woman meeting our inclusion criteria enters the cohort at the end of her first trimester. Study participants receive a total of three online questionnaires covering sociodemographic characteristics, travel behaviour patterns and lifestyle. Participants complete these questionnaires at recruitment, during the second and third trimester. The level of personal exposure to air pollution is characterised using a dynamic spatiotemporal trajectory model that describes the main daily movements of pregnant women and the time spent in each place frequented. Univariate, multilevel and Bayesian

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our cohort study design will allow us to evaluate the pregnancy exposome and birth outcome.
⇒ Our cohort provides a unique opportunity to investigate various exposome aspects.
⇒ The participation of only French-speaking women could be a limitation of the ability to extrapolate results.
⇒ Data collected from some questionnaires (Pregnancy Physical Activity Questionnaire) could be affected by recall bias.

model will be used to investigate the relationships between exposome characteristics and the health status of pregnant women and their newborns.

Ethics and dissemination Our research was approved by the Commission de Protection des Personnes (CPP) Ile de France VI (Paris) on 9 December 2020 (File reference No. 20.09.15.41703 ID RCB: 2020-A02580-39 and No. 20 080–42137 IDRCB 2020-A02581-38). The Agence Nationale de Sécurité du Médicament was informed of it on 15 December 2020. Findings from the study will be disseminated through publications and international conferences and through presentation at meetings with local stakeholders, researchers and policy-makers.

Trial registration numbers NCT04705272, NCT04725734

BACKGROUND

Context

Adverse pregnancy outcomes, including the health status of both pregnant women (eg, gestational weight gain, diabetes) and newborns (eg, low birth weight (LBW), preterm birth (PTB)) now constitute a crucial health problem in many European countries, representing a public health challenge. For instance, according to the European Perinatal Health Report, in most north European

countries LBW occurs in less than 4.5% of all births—yet in France and Spain, this figure is closer to 10%. The LBW percentage also appears to have increased between 2010 and 2015.[1] Moreover, the burden of gestational diabetes is estimated at 170 cases per 1000 live births, and this is expected to rise further as a result of the increasing prevalence of excess weight and obesity during pregnancy.[2] Adverse pregnancy outcomes and their consequences (including adverse birth outcomes) also contribute significantly to overall health costs.[3–6]

According to the European Union benchmarking report for 2009/2010, statistical data collected from 14 European countries demonstrates the significant and growing cost of prematurity in Europe. For instance, in Denmark the average cost of a preterm birth was €55 460, while in France, the total cost amounts to more than €1.5 billion each year.[7] However, the risk factors for adverse pregnancy outcomes are yet to be completely understood, though the aetiology is thought to be multifactorial.[8] It also remains unclear whether these adverse pregnancy outcomes could result from determinants acting either independently or in an inter-related manner.[9 10]

The identification of social and environmental risk factors therefore represents a crucial step towards developing (and effectively targeting) interventions aimed at preventing adverse pregnancy outcomes.

Current knowledge
The first 1000 days of life
A growing body of evidence confirms that lived experience during the first 1000 days of life can be a critical determinant of a child's likelihood of survival, growth and level of well-being during both childhood and adulthood. Fragile newborns are particularly sensitive to the quality of their living environment[11] and because neurodevelopmental, biological and hormonal changes are taking place during this period, these processes can be affected by environmental factors.[12] The healthy development of the child during the first 1000 days is thus strongly related to maternal health status during pregnancy, residential living conditions and neighbourhood characteristics—including socioeconomic status. More precisely, maternal health status during pregnancy, including excessive gestational weight gain (EGWG), gestational diabetes mellitus and obesity, is known to have significant consequences for newborn mortality and morbidity,[13] including preterm birth.[14] For instance, a wide literature supports the idea that exposure to ambient air pollution in pregnancy is associated with adverse pregnancy outcomes, especially with regard to fetal growth and gestational duration.[15–21] Exposure to air pollution during pregnancy has been shown to be associated with reduced birth weight[22] and reduced postnatal lung function, as well as lung function between the ages of 5 weeks and 11 years.[23 24] Ambient air pollution exposure is posited to affect the fetus either directly (via transplacental exposure) or indirectly (by effecting physiological changes in the mother).[13] In addition, neighbourhood characteristics (such as walkability

and green spaces) are associated with pregnant women's health status, including lower risk of diabetes[25 26]—a disease that can lead to serious adverse birth outcomes, such as LBW and PTB.

During the first thousand days of life, then, pregnant women, fetuses and newborns are exposed daily and simultaneously to a multitude of factors, including maternal or fetal medical conditions, genetic influences, infertility treatments, behavioural, iatrogenic prematurity, community resources and environmental exposure.[9 10] These environmental factors have been associated with the health status of both pregnant women and newborns.

Exposome and pregnancy
In 2005, Wild developed the concept of the exposome to describe the total sum of all environmental exposures, from conception to death.[27] The exposome is defined as being key to understanding the complexity of the association between environmental exposures and the rise in chronic diseases. Exposome includes external factors (both specific and general) as well as internal factors.[28] General external factors of the (non-specific) exposome are focused on pregnancy exposure to a set of environmental nuisances (eg, air pollution, noise, environmental amenities, climate) that may affect the health status of both pregnant women and newborns. For instance, since green spaces may have beneficial effects on birth outcomes and child development,[22–24] these can reduce the incidence of both excessive weight gain and gestational diabetes during pregnancy.[29] Moreover, exposure to air pollution has been associated with reduced birth weight and decreased lung function in children, while noise exposure has been associated with raised blood pressure in children.

Specific external factors include diet, healthy behaviours, lifestyle choices and socioeconomic status. For instance, physical activity (PA) in pregnant women has been shown to have beneficial effects on both maternal health status and neonatal outcomes, including the reduction of EGWG and a reduced risk of hypertensive disorders[30–32] as well as improvements to the child's cognitive development.[33 34]

Recently, at the European level, the Human Early Life Exposome project has tended to characterise urban exposome and its relationship to child health and development across nine birth cohorts.[35] Urban exposome is defined as the set of air pollutants, noise, meteorological factors, green spaces and built environment characteristics (urban spaces, buildings design, parks, transportation systems and walkways) to which people are exposed in the urban environment, and can be assessed using common geospatial methods.[36]

Hypotheses and objectives
The aim of our project is to explore the relationships between exposome characteristics and the health status of pregnant women and their newborns. In particular, this study addresses the following question: in terms of

the disparities observed in the health of pregnant women and newborns, what roles are played by environmental exposure, access to amenities, and socioeconomic characteristics? More specifically, we are studying the relationships between the social inequality of adverse pregnancy outcomes and (1) short-term exposure to atmospheric pollution (MobiFem project) and (2) pregnancy lifestyle (EnviFem project).

Our hypothesis is that deprived neighbourhood characteristics, combined with adverse environmental characteristics (in terms of exposure environment, green space and the built environment) may influence the health status of pregnant women and newborns. To test this hypothesis, we are investigating the relationship between neighbourhood characteristics, socioeconomic environment, and maternal and newborn health within a cohort of pregnant women.

METHODS AND ANALYSIS
Study design
This is a prospective, observational and multisite cohort study of pregnant women involving the Strasbourg University Hospital (CHRU), across two sites, namely the Hautepierre Maternity Hospital (HTP) and the Obstetrics Medical and Surgical Centre (CMCO). With more than 70% of deliveries in the Strasbourg metropolitan area taking place at this hospital, it was chosen with a view to achieving broad coverage of socioeconomic characteristics among the women.

Study population and recruitment
The study population is the group of eligible mothers living in the Strasbourg metropolitan area who have agreed to take part in the study. According to National Institute for Statistics and Economic Studies (INSEE), the urban area of Strasbourg is made up of 267 municipalities, 265 of which are located in the Bas-Rhin and 2 in the Vosges. It is the 9th largest urban area in France with 802 437 inhabitants in 2019. The calculation of the number of subjects needed to be included in the cohort was estimated at 600 patients. Trained research personnel obtain informed written consent from participants.

Recruitment began in February 2021 and will be complete by December 2021; inclusion and exclusion criteria are described in table 1. Participants were recruited from weekday, first trimester, antenatal ultrasound appointments at both sites. Pregnant women meeting the inclusion criteria enter the cohort at the end of the first trimester (see table 1).

At their first scan appointment, invitations to take part in the study are made via a letter providing information about the study and its aims. At the same time, to make matters as clear as possible, women are also provided with information orally. At the same day, once they have signed the consent letter and returned it to the research team, they are included in the cohort.

Patient involvement
Pregnant women were involved in creation and correction of questions during the test phase of the questionnaire. Patient and public were not involved in design and conduct of the study, the choice of outcome measures or the recruitment.

Setting
The setting of our study is the Strasbourg metropolitan area in eastern France, which covers a total area of 337.61 km^2. According to the 2016 national census, this Eurometropolis of Strasbourg is home to 491 409 inhabitants across 33 municipalities. To characterise the neighbourhood in which each participant lives, we have chosen to define the spatial delimitation of the residential neighbourhood at census block level. This study is thus being performed at the level of the submunicipal geographical unit IRIS (Ilots Regroupées pour l'Information Statistique). The IRIS is a statistical unit used for the French census; a residential block defined by the INSEE. Each French municipality is thus subdivided, according to its demographic and geographic size, into one or more blocks (with an effective mean of 2000 inhabitants). The

Table 1	Participant inclusion and exclusion criteria
Inclusion criteria	► Age (≥18 years) ► Women whose first trimester of pregnancy falls between February 2021 and February 2022 ► Pregnant women living in the Strasbourg metropolitan area ► Pregnant women who had registered their pregnancy and received subsequent antenatal care in University Hospitals of Strasbourg singleton pregnancies ► Women having adequate knowledge of spoken and written french language
Ineligibility criteria	► Women unwilling or unable to give informed consent ► Women under the protection of a legal guardian, guardianship, curatorship, etc ► Women declining to take part
Exclusion criteria	► Threatened preterm delivery ► Placenta praevia (low-lying placenta) ► Pre-eclampsia ► Pregnant women having the following obstetric pathology in current pregnancy

Strasbourg metropolitan area is subdivided into 190 such blocks.

Ethical approval

Our research was approved by the Commission de Protection des Personnes (CPP) Ile de France VI on 9 December 2020 (File reference numbers 20.09.15.41703 ID RCB: 2020-A02580-39 and 20 080-42137 IDRCB 2020-A02581-38) and the Agence Nationale de Sécurité du Médicament (ANSM) was informed on 15 December 2020. Since this non-interventional research carries no risks or constraints, all procedures are performed, and products used, in the usual way. The research is subject to the provisions of Articles L 1111-7 et seq., L1121-1 et seq., as well as to those of Articles R 1121-1 et seq. of the Code de la Santé Public.

Once researchers have explained the modalities of the research, patient consent is obtained via signature of the letter of no objection.

The data processing implemented within the framework of this research is conducted in compliance with French Law No. 78-17 of 6 January 1978 relating to data processing, files and freedoms modified by French Law 2004-801 of 6 August 2004. This research falls within the framework of 'Reference Methodology' (MR-003) in application of the provisions of Deliberation No. 2016-263 of 21 July 2016. The research sponsor has undertaken to comply with this Reference Methodology, dated 24 October 2016. Eligible women (along with the fathers of their children) are asked to provide signed consent to participate in the study, and are provided with a copy of this.

Study protocol

All participants are invited, at the time of enrolment, to respond to questionnaires during the first, second and third trimester, and will therefore be followed up until delivery. Participants are identified by study number only; no identifying information is to be transferred beyond the participating hospital site.

The research team at CHRU will collect data on health outcomes and individual characteristics from pregnancy registries, clinical records and the specific questionnaires (administered by email) to participants involved in our study.

Data are being collected via either online software-administered questionnaires (LimeSurvey V.3), or (where women were unfamiliar with computer software and/or have difficulties reading) via phone interview with the researcher. In addition, anthropometric measurements are being collected via analysis and review of electronic hospital records. Data collection tools and methods are detailed below. Data on each of these outcome variables are collected at each time point (see table 2).

Questionnaires

These questionnaires are content-validated, French territory-adapted and pilot-tested, and have been revised for use in this study among pregnant women. The final revised questionnaires were self-administered.

All participants receive a total of three questionnaires: (1) the day of their first scan appointment, after enrolment, participants receive an online questionnaire on demographic characteristics, travel behaviour patterns and lifestyle; (2) during the second trimester of pregnancy, participants receive an online questionnaire addressing any changes in travel behaviour patterns and lifestyle; (3) during the third trimester, participants receive an online follow-up questionnaire addressing any changes in travel behaviour patterns and lifestyle. If participant not respond to one or more of the questionnaires, we contact her by mail to ask to complete the questionnaire and/or we propose to help her to complete the questionnaire by phone. if a participant decides to leave the cohort study and not response to questionnaire, then we consider that the participant has drop out.

At the time of study enrolment, the data collected on each patient includes:
1. Baseline sociodemographic characteristics, maternal lifestyle data during each trimester of pregnancy, via the Pregnancy Physical Activity Questionnaire (PPAQ), a perceived quality of life score via the Short Form Health Survey (SF36), and daily mobility data, via questionnaire.
2. Clinical and medical data from hospital records.
3. Neighbourhood characteristics (including air pollution and environmental amenities).

All data collection tools are detailed below.

Maternal sociodemographic characteristics

Individual information is collected via a predesigned datasheet (online supplemental appendix 1); this includes demographic information (maternal age and infant sex), with additional socioeconomic characteristics for the pregnant women—such as occupational category, level of education and employment status.

Medical information

Perinatal data are collected from hospital records. The information collected includes parity, gravidity, date of conception, delivery date, body mass index, weight gain at the end of pregnancy, newborn health status, Apgar score, obstetric pathologies, mode of delivery, gestational age, sex, anthropometry including fetal weight and length, head circumference, birth weight and growth percentile using ultrasound data.

Maternal lifestyle

Women complete the Short Questionnaire to Assess Physical Activity at study entry (trimester 1), between the 22th and the 28th weeks of pregnancy, and between the 32th and 38th weeks of pregnancy. Because it has already been validated in a pregnant population, the PPAQ is used to estimate participants' PA.[37] The French version of the PPAQ has been used and validated in Canadian and Swiss studies.[38] The semiquantitative PPAQ includes

Table 2 Data collection

Detailed information	Investigation tools	Pregnancy trimester			Delivery
		First Between 11 and 17weeks of amenorrhea (WA)	Second between 22 and 28 WA	Third between 32 and 38 WA	
Inclusion					
Mother: 18 years, ultrasound and delivery at HTP or CMCO, speaks and understands French language	Singleton pregnancy	√			
Maternal					
Anthropometry Height, prepregnancy weight, weight in each trimester and predelivery	Hospital records	√	√	√	√
Sociodemographic characteristics Age, occupation, education, parity, income, marital situation, spouse education and occupation	Administered questionnaire	√	√	√	
Smoking, alcohol	Administered questionnaire				
Place of residence, weekday and weekend mobility	Administered Questionnaire-Maternal mobility	√	√	√	
Life quality	Administered questionnaire				
Physical activity	PPAQ	√	√	√	
Perception of the living environment	SF36	√	√	√	
Exposure to air pollution (NO$_2$, PM$_{10}$, PM$_{2.5}$)	Modelisation approach				
Perinatal information					
Pregnancy complications (gestational diabetes, premature delivery threat, pre-eclampsia)	Hospital records				√
Delivery					
Duration of labour	Hospital records				√
Delivery method	Hospital records				√
Delivery complications	Hospital records				√
Newborn					
Sociodemographic characteristics Gestational age, birth date, sex of infant	Hospital records				√
Anthropometry Fetal weight and length, head circumference, birth weight, percentile of growth on ultrasound	Hospital records				√
Evaluation Apgar	Hospital records				√

CMCO, Obstetrics Medical and Surgical Centre; HTP, Hautepierre Maternity Hospital; PPAQ, Pregnancy Physical Activity Questionnaire; SF36, Short Form Health Survey.

32 questions on the amount of time spent on various categories of PA. This self-administered questionnaire can be easily understood by respondents in a variety of settings, and takes approximately 10 min to complete. Each pregnant woman is asked to recall and report her PA over the past 7 days. The PPAQ asks respondents to report time spent on 32 activities, including household/caregiving activities (13), occupational activities (5), sports/exercise activities (8), commuting activities (3) and inactivity.[39] For each activity type, they are asked to enter the time spent per day or week (minutes or hours per day or per week). Each activity is assigned an intensity level using the metabolic equivalent (MET). The MET is a unit traditionally used to estimate the metabolic 'cost' of PA. The self-reported time spent on each activity is multiplied by specific intensities to obtain average energy expenditure per week (MET-hours/week). Each activity is then categorised into one of four groups: sedentary, light intensity, moderate intensity and vigorous intensity. In addition, participants are categorised into two groups (active or

inactive) based on the American College of Obstetricians and Gynecologists recommendations.

Maternal quality of life

Perception of the living environment is evaluated using a prevalidated and prepublished questionnaire[40] that allows us to evaluate perception of residential neighbourhood, modes of travel and of pregnant women in their home environment. A single such evaluation is conducted during the pregnancy.

Health-related quality of life is also measured, using the French version of the SF36 which assesses eight aspects of health: (1) limitations in PAs due to health problems (10 items); (2) limitations in social activities due to physical or emotional problems; (3) limitations in usual activities due to physical health problems; (4) physical aches and pains; (5) general mental health (psychological distress and well-being); (6) limitations in usual role activities due to emotional problems; (7) vitality (energy and fatigue) and (8) general health perceptions.[41] Participants complete the SF36 Questionnaire at study entry (trimester 1), between 22 and 28 weeks of pregnancy, and between 32 and 38 weeks of pregnancy.

Maternal travel behaviour patterns

Estimates of participant mobility are performed using a behaviour questionnaire on travel patterns. As mentioned above, these behaviour questions are administered three times during pregnancy: at enrolment, between the 22th and the 28th weeks of pregnancy and between the 32th and 38th weeks of pregnancy. Each pregnant woman is asked about their typical behaviour patterns in terms of everyday travel (including working and non-working days) over the past 3 months.

The information we collect includes residential address, work locations and three other destinations at which women spend most time on weekdays, as well as two main destinations where women spend most time at weekends (eg, places of leisure, supermarket, school, other).

For each trip and each destination, the questions also cover point of departure, departure and arrival times, how long participants spend at their destination and the modes of transport they use.

In addition, the questions cover mode of transport from home to different destinations, trip duration and distance from home to various destinations and commuting in both directions. Average in-vehicle travel time is also recorded (including different modes of transport used, eg, underground, bus). The questions used to assess women's mobility are described in online supplemental file 1.

Measurement of outcomes

Mobifem project: adverse birth outcomes

Birth weight outcome is assessed using the WHO definition of LBW: birth weight less than 2500 g (referenced P07.0–P07.1 in the 10th revision of the International Classification of Diseases-ICD 10).[42] Gestational age is assessed using PTB, defined as childbirth occurring at fewer than 37 completed weeks (or 259 days) of gestation (reference P07.2–P07.3 in ICD 10). Fetal weight, length, head circumference, birth weight and growth percentile (from ultrasound) are also used to assess newborn health status.

Envifem project: adverse pregnancy outcomes

Adverse pregnancy outcomes are gestational diabetes and gestational weight gain (the difference between weight at the beginning and end of pregnancy). Obstetrical pathologies (threatened preterm labour and complications at delivery) and postpartum haemorrhage, caesarean and obstetric perineal tears are also used to assess obstetric outcomes, as well as duration of labour.

Maternal exposure assessment

Three pollutants were selected for this study, namely nitrogen dioxide (NO_2), particulate matter with an aerodynamic diameter equal to or less than 10 μm (PM_{10}) and particulate matter with an aerodynamic diameter equal to or less than 2.5 μm ($PM_{2.5}$).

The level of personal exposure to air pollution is characterised using a dynamic spatiotemporal trajectory model describing the main daily movements of pregnant women and the time spent in each place frequented. The process design tools for estimation of weekly exposure to air pollution mainly consists of three steps.

First, the individual daily mobility to the most frequented places will be been taken into account to compute different realistic itineraries of each trip. The set of routes will be calculated by weighting the shortest routes calculation, based on the Dijkstra algorithm. Using the build transport network and the home addresses and frequented places, we obtain several itineraries for each origin/destination pair.

Second, for each participant, we will estimate sets of hourly exposure to pollutants for each trip, based on spatial and temporal metrics. We will generate estimates of hourly concentrations of pollutants obtained from the dispersion model. Modelled data will be obtained from ATMO Grand-Est, a local organisation that monitors air quality in the Eurometropolis of Strasbourg. Hourly concentrations will be estimated at the various locations at which the woman has spent time, using the model ADMS-Urban of Cambridge Environmental Research Consultants, which integrates multiple parameters: road network, industrial emissions, meteorological and topological data.

Finally, we match each participant's daily travel pattern with an hourly concentration of the three pollutants modelled. In our dynamic model, we estimate the pregnant women's daily exposure concentrations by arithmetically weighting concentrations at different places frequented, based on how long women spent at each location and the modes of transport they used. This allows us to estimate for each scenario of itineraries' daily concentration of air pollution Once each woman's exposures

have been estimated per day of measurement, we will extrapolate average daily exposure to weekly exposure, then to trimester estimates.

This assessment methodology was validated in our previous study (for more detailed information, see Pozzar M. 2021).[43]

Characterisation of environmental amenities during pregnancy

Residential neighbourhood characterisation is based on two aspects: (A) Objective measurement of the physical environment.

Our study uses five geographical indicators to characterise the built environment assessed in our previous study[44]: (1) an elaborate public transportation supply indicator, (2) a typology of the territory aimed at quantifying and qualifying the availability of sports facilities, (3) an indicator measuring accessibility to green spaces, (4) a composite indicator describing commercial potentiality, (5) a typology of land use characterising both density and the mix of the urban form around the homes of pregnant women. (B) Socioeconomic environment.

We use a validated and published indicator of socioeconomic disadvantage[45] to characterise the neighbourhood in which the mothers live during pregnancy. This index, developed in our previous study,[45] is constructed from 15 socioeconomic and demographic variables collected by the National Institute of Statistics and Economics (for more detail, see Lalloué et al[45]).

Statistical analysis plan

First, multilevel analysis models will be used to investigate the association between neighbourhood characteristics and the PA of pregnant women. Three different models are to be implemented: Models 0 and 1 consider individual data only, while model 2 combines both individual and census block data (neighbourhood characteristics). Regression coefficients (beta) will be estimated, using both classical (model 0 and Model 1) and multilevel (model 2) linear regressions for associations between PA and explanatory variables, while classical (model 0 and model 1) and multilevel (model 2) logistic regressions will be used for recommended PA (ORs will be produced with a 95% CI). Two different indicators will be used to quantify between-census-block variations. Variations in PA will be assessed using the intraclass correlation coefficient. Median ORs (MORs) will be computed to translate between-census-block variation in recommended PA risks into an OR scale. Data will be analysed using STATA V.16 (StataCorp).

Second, to take into account the correlation between participant characteristics, generalised estimating equations models will be used to quantify the association of PA and GWG/diabetes. All statistical analyses will be conducted with an alpha risk equal to 5%. All the models will be estimated in SAS, using full-information robust maximum likelihood (MLR) as our estimator.

Lastly, we will use Bayesian Distributed Lag Interaction Models BDLIM, which extends the traditional DLM framework to the examination of associations between pregnancy exposure and birth weight and the identification of sensitive windows for the effects of prenatal exposure to outdoor pollution by estimating the time-varying association of each participant's weekly averaged exposures throughout the gestational period. In addition, we will examine how this relationship is modified by newborn sex. All models will be adjusted for newborn and maternal characteristics. All analyses will be implemented in R statistical software (V.3.3.1), using R package regimens (REGression In Multivariate Exposure Settings).

Since our study will include two centres, our statistical analyses will test the adjusting for centre. First, we will pool all centres data and adjusting for centre using fixed effects. In the second step, we will fit model using random effect where we assume that the within-centre relationship between Y and X is the same as the between-centre relationship between Y and X, and that these two relationships can be combined into a single estimate of beta.

In addition, spatial model may be based on clustering approach[43] to investigate to what extend neighbourhood characteristics may partially explain the geographical distribution of pregnancy outcome.

As mentioned above, one of the main purpose of the MOBIFEM and ENVIFEM aim to explore the relationship between neighbourhood characteristics and pregnancy outcomes according to socioeconomic status. We will fit 9 (3×3) separate models to cover all combinations of dependent variables and to capture the interaction between socio economic status and exposition level on the one hand, and socioeconomic status and neighbourhood characteristics in other hand. Based on the number of covariates and interaction term tested, the target sample size of 600 patients would be adequate to conduct statistical analysis and to reach a target sufficient statistical power.

ETHICS AND DISSEMINATION
Ethical approval

Our research was approved by the Commission de Protection des Personnes (CPP) Ile de France VI on 9 December 2020 (File reference numbers 20.09.15.41703 ID RCB: 2020-A02580-39 and 20 080-42137 IDRCB 2020-A02581-38) and the ANSM was informed on 15 December 2020. In this non-interventional research carrying no risks or constraints, all procedures are performed, and products used in the usual way. It is subject to the provisions of Articles L 1111–7 et seq., L1121-1 et seq., as well as to those of Articles R 1121–1 et seq. of the Code de la Santé Public. Once researchers have explained the modalities of the research, patient consent is obtained via signature of the letter of no objection.

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