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# Assessing the risks for stillbirth in São Paulo, Brazil: protocol for a multidisciplinary case–control study – FetRisks

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## ABSTRACT

Stillbirth is a fundamental component of childhood mortality, but its causes are still insufficiently understood. This study aims to explore stillbirth risk factors by using a multidisciplinary approach to stimulate public policies and protocols to prevent stillbirth, improve maternal care and support bereaved families.

**Methods and analysis** In this case–control study with stillbirths and live births in 14 public hospitals in São Paulo, mothers are interviewed at hospitals after delivery, and hospital records and prenatal care registries are reviewed. Maternal and umbilical cord blood samples and placentas are collected to analyse angiogenesis and infection biomarkers, and the placenta's anatomopathological exam. Air pollutant exposure is estimated through the participant's residence and work addresses. Traditional and non-invasive autopsies by image-guided histopathology are conducted in a subset of stillbirths. Subsample mothers of cases are interviewed at home 2 months after delivery on how they were dealing with grief. Information contained in the official prenatal care registries of cases and controls is being compiled. Hospital managers are interviewed about the care offered to stillbirth mothers. Data analysis will identify the main risk factors for stillbirth, investigate their interrelations, and evaluate health services care and support for bereaved families. We hope this project will contribute to the understanding of stillbirth's risk factors and related health services in Brazil, providing new knowledge about this central public health problem, contributing to the improvement of public policies and prenatal and puerperal care, helping to prevent stillbirths and improve the healthcare and support for bereaved families.

**Ethics and dissemination** This study protocol was approved by the Ethics Committee of the Municipal Health Secretary (process no 16509319.0.3012.5551) and of the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (process no 16509319.0.0000.0068). Results will be communicated to the study participants, policymakers and the scientific community.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study explores the causes of stillbirth in Brazil through multiple approaches, including interviews, fetal autopsies, biomarkers, prenatal and hospital records, and air pollution data analysis.
⇒ This multidisciplinary study articulates epidemiological and clinical knowledge on stillbirth risk factors to recommend cost-effective interventions.
⇒ This study encompasses 14 public hospitals in São Paulo, therefore, limiting the results' translation to private healthcare settings.
⇒ The complexity of stillbirth's contributing causes and the multiplicity of study variables are challenging to consider in epidemiological studies and will require the use of complex statistical analyses.

## INTRODUCTION

Despite a growing body of evidence on the impacts of stillbirth and its associated risk factors, most come from high-income countries, while in low-income and middle-income countries (LMICs), where 89% of stillbirths occur, this event is still undervalued and insufficiently studied.[1] Stillbirth reduction was not properly addressed in the Sustainable Development Goals, despite its invaluable impacts on child and maternal health, and a less favourable evolution of this indicator

globally.[2] However, some global initiatives aimed to accelerate progress on reducing stillbirths by 2030 were proposed by improving data collection, expanding research, advancing the knowledge of causal mechanisms, and linking biological and epidemiological factors of stillbirth.[3 4]

An important challenge for stillbirth studies is to determine the causal pathways of death.[5] This is more significant in LMIC, where investigation procedures and data collection tools are not always standardised, and trained healthcare workers (HCWs), adequate technological resources and perinatal death audits are lacking, leading to important under-reporting and misclassification of stillbirths.[1 4]

Epidemiological studies have identified several maternal and fetal risk factors associated with stillbirth globally, including maternal biological, demographic, familial and psychosocial characteristics, such as overweight and obesity, diabetes, hypertension, mother's advanced age, low educational level, poverty, race, single marital status or with a recent partner, undernutrition, smoking habits, as well as premature or prolonged pregnancy, primiparity and obstetrical complications, such as bleeding, pre-eclampsia/eclampsia, child growth restriction, placental pathologies, membranes' rupture, congenital malformation and placental abruption.[2 6–10] The number of antenatal visits, prenatal and delivery care access and quality,[6–9 11] and the healthcare guidance offered to mothers regarding the identification of decreased fetal movements, timely and effective access to a health service in pregnancies over 41 weeks[12 13] were associated with the risk of stillbirth. Moreover, exposure to air pollution[14 15] and infectious agents[2 9] are also recognised issues.

In Brazil, some studies had focused on stillbirths, but most relied on analysing secondary data from death certificates and health information systems, the quality of information, and national, regional, or local temporal rates and trends. Among those addressing stillbirth's death causes, most were descriptive and limited to the 10th International Classification of Diseases and Related Health Problems (ICD-10) causes informed in the death certificate or evaluated the classification system used and the information level while less attention was given to the risk factors and associated conditions.[10] São Paulo, which is the largest city in South America, lacks comprehensive evidence on stillbirth's risk factors. Moreover, studies that analyse the conditions of prenatal care and delivery of stillbirths are also lacking in Brazil and São Paulo, as well as studies on the impact of stillbirths from the individual, familial and social perspectives, indicating the need for a better understanding the stillbirths causes and healthcare services provided during pregnancy, and after a stillbirth.[10]

In 2017, the stillbirth rate in the municipality of São Paulo (MSP) was 8.7 stillbirths per 1000 births, with a 6% increase from 2007 to 2017. In the same year, there were 1286 stillbirths compared with 1894 infant deaths. However, stillbirths represent 60% of the perinatal deaths in the MSP.[16] Almost all stillbirths occur in hospitals and the vast majority are antepartum, weighing <2500 g and undergo necropsy to determine the cause of death. Even so, 25% of stillbirths continue to be classified as unspecified, indicating the need to improve the understanding of mortality conditions and causes.[17] Although half of São Paulo's population is covered by private healthcare, public hospitals of the Unified Health System (SUS) account for approximately 60% of childbirth care and over 75% of stillbirths.[18–20]

The multiplicity and complexity of the different risk factors related to stillbirth and the way these factors relate to each other make it difficult to consider them together in epidemiological studies and to effectively prevent it. Also noteworthy is the lack of detailed information in the Brazilian context on the contribution of diverse risk factors to stillbirth, which is an important subsidy for public policy proposals. In this sense, this research project aims to identify the contributing causes of stillbirth in São Paulo, Brazil, elucidate the role of biological mechanisms, maternal infections and air pollution exposure on stillbirth, analyse healthcare services, especially those related to prenatal and delivery care and support for dealing with grief, and to explore new statistical approaches applied to the multicausal aetiological mapping of stillbirth, and family's grief and context.

## METHODS

### Study design and population

This is a population-based case–control study, in which cases are stillbirths and controls are live births that occurred in one of the 14 public hospitals in São Paulo participating in the study (figure 1).

São Paulo, located in Southeast Brazil, has 11 451 245 inhabitants, while its Metropolitan Region of São Paulo (MRSP) has almost 21 million inhabitants. São Paulo has a high per capita income and low illiteracy rates,[21] but an important social inequality, especially in the city's outskirts, which may partially explain the higher stillbirth rates observed in these areas.[17] Moreover, the MRSP has some recognised risk factors that are investigated in this study, such as unequal distribution of health services,[22] high levels of air pollution, especially across lower-income neighbourhoods,[23] as well as a growing incidence of maternal and congenital syphilis.[24 25]

### Inclusion and exclusion criteria

Women with stillbirths are invited to join the study in the participating hospitals. Controls are live births occurring subsequently to the stillbirth at the same hospital. In Brazil, stillbirths are classified based on the WHO ICD-10 definition, which is 'the death of a fetus that has reached a birth weight of 500 g, or if birth weight is not available, a gestational age of 22 weeks'.[26] Thus, we included only singleton stillbirths and live births of women residing in the MRSP, with gestational age ≥22 weeks and ≤44 weeks or weighing ≥500 g. Live births that died in the delivery

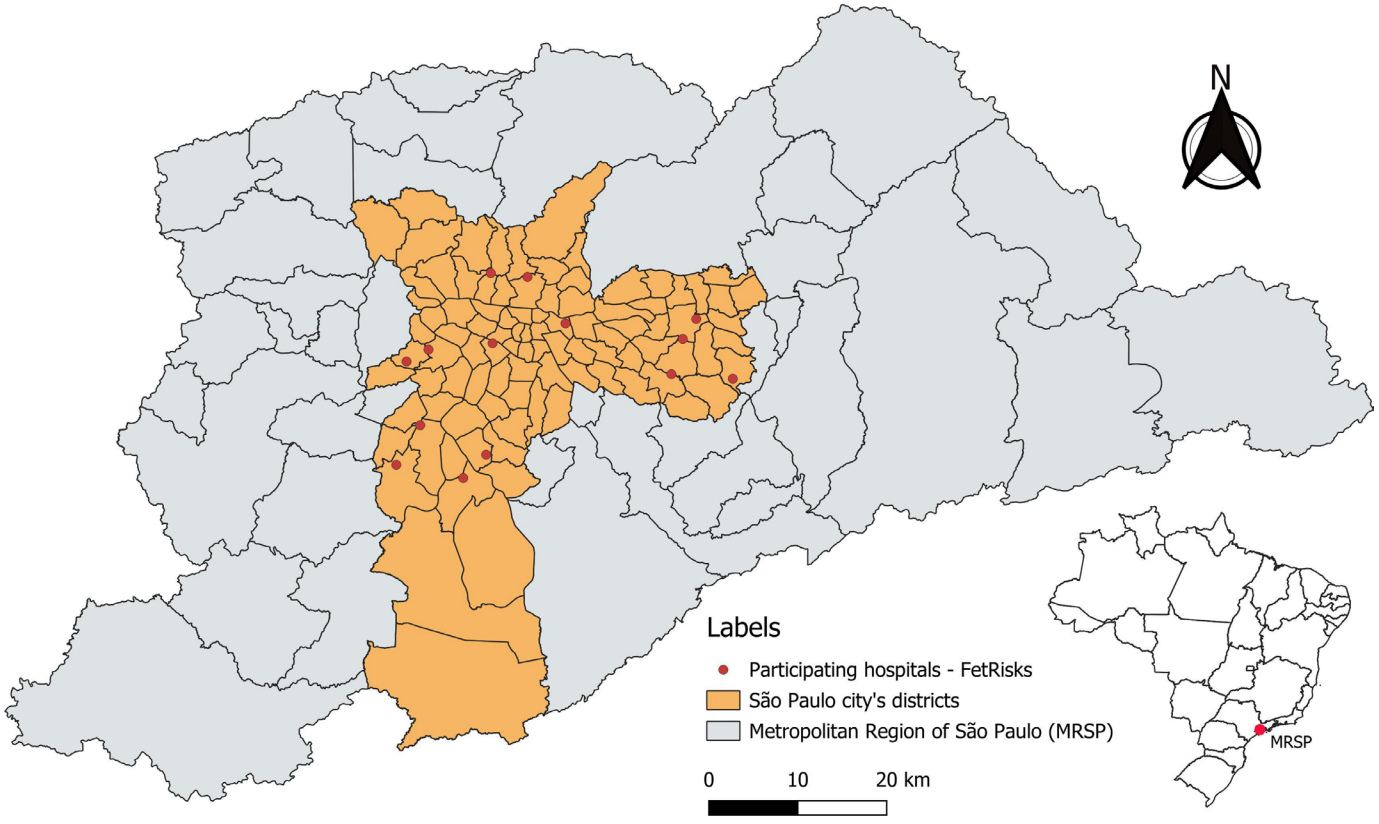


**Figure 1** FetRisks' study location, São Paulo, Brazil.

room, stillbirths from legally interrupted pregnancy and those below 22 weeks and weighing less than 500 g were excluded. These definitions follow the ICD-10 and are used by local health services to issue the death certificate and to perform the autopsy. It aims to exclude very early neonatal mortality (<20 weeks), avoid possible misclassification and recording errors, and ensure robust ORs for a low prevalence event, such as stillbirth.

### Sample size calculation

The sample size was established as one control for each case, due to financial and logistical constraints by using a confidence level of 95% (1–α), to detect OR values of 1.70, with test power of 80% (1–β), assuming an exposure of 10% for the controls, based on the continuity correction,[27] and the calculated sample size was 395 cases and 395 controls. To deal with possible losses and exclusions (5% of estimated losses), 415 stillbirths and 415 live births are being considered, totalling 830 events.

To estimate the sample size, we considered any of these three important risk factors for fetal deaths: maternal diabetes, hypertension and prevalence of congenital malformation. This was defined after examining Brazilian case–control studies on stillbirths that indicated that each of these three risk factors had a prevalence of around 10% among controls.[7 28] Thus, the sample size was calculated considering a prevalence of exposure among controls of 10%. This sample size will allow us to examine these three exposures and any other with a higher frequency with an OR of at least 1.7. However, the study will not have the power to identify associations with less frequent exposures or for factors with smaller risks in the general model. Even so, it may be possible to identify subsamples in which the exposure is more common or has a higher risk, for example, insufficient prenatal care might carry a higher risk in women with diabetes or hypertension. The final analysis will be hierarchical, reflecting a causal framework based on biological mechanisms and may include subgroup analyses. The formula used to estimate the sample size and its parameters were included as online supplemental material 1.

### Hospitals' selection

In total, 14 public hospitals in the MRSP were selected to participate in the study based on the frequency of deliveries and stillbirths, complexity of health services and geographical location, to include different regions, representing the spatial distribution of exposures and outcomes throughout São Paulo, and facilitate the logistical aspects of conducting interviews, accessing hospital records, and obtaining and transporting biological samples for analysis. Thus, hospitals with a small volume of deliveries that resulted in stillbirths were excluded.

### Data storage and management

An electronic software was developed for data recording, storage, and management, and to help administrating the field data collection. The system has distinct modules, including the participant's registry (cases and controls); control of biological samples collected (maternal blood,

umbilical cord blood, placenta and fetus); mother's questionnaires (general and bereavement interviews); patients' records review; prenatal care registries; death verification reports (fetal autopsy) and results of lab tests.

A pretest of the data collection instruments and data storage application was carried out in two participating hospitals, showing that the instruments were adequate, as was the established flow for obtaining and analysing the biological material. An important change made at this point was the inclusion of specific questions related to COVID-19 diagnosis, testing, hospitalisation and serological tests provided.

### Fieldwork strategies and procedures

All participating hospitals received face-to-face training before starting data collection, and several in-person and online training with newly hired HCWs who were unfamiliar with the study. In these training, the research procedures, protocols, informed consent forms and risks were discussed with the HCWs who are present at the time of delivery, who can identify eligible cases and have all the inputs necessary for the data collection. The material was also sent to the HCW responsible for data collection so they could review it when necessary. To facilitate communication and optimise data collection, a Whatsapp group was created for each hospital, with everyone involved in data collection. Recurrent meetings with hospital managers and HCWs are also being held to strengthen ties and stimulate adequate data collection.

Moreover, participating hospitals were provided with an identified toolbox with the terms of consent, and all materials necessary to collect, store and transport the biological samples to partner laboratories for analysis (eg, tubes for blood collection, syringes and needles, plastic bags to store the placenta, 10% formaldehyde and dressings), as well as barcode labels to identify the samples and a minibar to store them, avoiding any additional cost to the hospitals.

The FetRisks study procedures include interviews with mothers, data collection from the prenatal care registries and hospital records, traditional and virtual autopsies of the fetus, examination of the placenta, blood analysis for the detection of infectious agents and angiogenic factors, and some specific secondary data analysis. After identifying a stillbirth in a participating hospital, a trained HCW, namely physicians and nurses, confirms the study's inclusion criteria and a form is fulfilled. If not, a case exclusion form is completed. If yes, mothers are informed about the study, have all the study's risks disclosed and are invited to participate. If one accepts to participate, she signs the informed consent form and has all samples (maternal and umbilical cord blood, placenta, and fetus) collected, identified, stored and sent for analysis. Project's field researchers are contacted, have the mother's basic information shared, and go to the hospital to interview the mother, and to collect the research documents. Similar procedures are performed for the controls, as described below.

Regarding participants' recruiting and retention, the study population consists of mothers who use public hospitals in Brazil, who, according to our knowledge and experience, are generally more willing to participate in research. The project team is providing feedback to the mothers about their fetal loss, another factor that provides greater acceptability to the study. Moreover, other than the subsample visited 1–2 months after the stillbirth to study coping mechanisms, there is no need to follow up patients as the questionnaire is only applied once, and patient record's data collection is made from the hospital records and prenatal care registries, thus excluding participant's retention concerns.

### Instruments and data sources

Data collection procedures were standardised through protocols, flow charts and guidance manuals for HCWs and field researchers to operate. Research procedures, instruments and data sources used are described below. Questionnaires and protocols used for mother's interview (online supplemental material 2); patient records' data collection—for cases (online supplemental material 3) and controls (online supplemental material 4); prenatal care registries (online supplemental material 5); bereavement interviews with mothers of stillbirths (online supplemental material 6); interviews with hospital's and midwives' managers (online supplemental material 7) and mother's informed consent forms—for cases (online supplemental material 8) and controls (online supplemental material 9) are included as online supplemental material.

#### Interview with mothers

Questionnaire-based interviews with mothers of cases and controls are being carried out in the hospitals during delivery hospitalisation, through electronic forms on tablets, in private rooms, by the project's field researchers. The questionnaire covers sociodemographic, economic and family characteristics (eg, education, income, housing conditions, marital status, occupation), maternal habits (eg, physical and leisure activities, and alcohol, tobacco and drug use), domestic violence, obstetric and reproductive history, and other health events before and during pregnancy (eg, body mass index, hypertension, diabetes, kidney and heart disease, infections, previous fetal loss, previous child with low birth weight or preterm birth, type of delivery, bleeding, eclampsia, placental disorders), assisted reproduction, medication use, psychosocial aspects (eg, acceptance of the pregnancy and unemployment during pregnancy), birth conditions, hospitalisations and health services use during pregnancy. For stillbirths, it is also investigated who communicated the death, and if the mother was admitted to the hospital or sent home. If necessary, this in-person interview can be supplemented by a telephone interview or by a scheduled home interview. In addition to the form, an instruction manual for administering the questionnaires was prepared.

### Patient records' data collection

Data from hospital records and prenatal care registries are obtained through a protocol to obtain information about obstetric history and the provided care during prenatal assistance, hospitalisation and delivery. From the prenatal care registries, information on gestational age, weight, lab tests, ultrasounds, medication, blood pressure, the presence of intrauterine growth restriction and congenital malformation is collected. This registry is a document filled out by HCWs during each prenatal care visit; it is presented to the health services during pregnancy and delivery hospitalisation and attached to the mother's medical records. Prenatal care registries are being scanned, and all information reviewed and entered into the project's electronic system as variables for later evaluation. Some information is contained in more than one instrument and these will be compared for consistency and quality. A manual was developed to standardise data collection, which is performed by trained field researchers. Hospital records are summarised according to a structured protocol.

### Biological sampling and analysis

Biological sampling is being carried out immediately after the delivery in the delivery room by the hospitals' trained nurses, and the placenta and blood samples of maternal and umbilical cords from all participants, and the stillbirth fetus are obtained. Maternal blood samples are collected in EDTA tubes (4 mL) and separating gel tubes (5+5 mL) and umbilical cord blood samples are collected in EDTA tubes (4 mL) and separating gel tubes (5 mL). These samples are identified and conserved in the freezer, before being handed over to field researchers to be sent to the Instituto de Medicina Tropical (IMT) of the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HCFMUSP) for analysis. The placentas and fetus are collected, identified and sent, respectively, to the Laboratório de Anatomia Patológica of the HCFMUSP, and to the municipal Death Verification Service (DVS) for analysis.

### Fetus's autopsy

Traditional autopsies are conducted by the DVS of the MSP, linked to the Departamento de Patologia of the Faculdade de Medicina, Universidade de São Paulo (FMUSP). Additionally, virtual autopsy, consisting of magnetic resonances, and tomography exams are being performed at the Imaging Platform in the Autopsy Room of the FMUSP on a subsample of the fetuses. These procedures were suspended by the COVID-19 pandemic crisis in 2020 and returned in 2022. The autopsies are performed by experienced technicians through established protocols.

### Placenta's analysis

After the expulsion, the placenta is placed in a 10% buffered formalin solution, fixed for 24 hours and analysed. The placenta's macroscopic examination consists of measuring the cord length and average thickness and three placental disc measurements. The placenta weight is measured after the membranes and umbilical cord removal. A roll of extraplacental membranes, umbilical cord sections, and at least eight sections containing the full thickness of normal-appearing placenta parenchyma are presented for histological analysis. Sections undergo routine processing, embedding, sectioning at 4µ and staining with H&E. When necessary, histochemical or immunohistochemical tests are performed for a more accurate diagnosis, such as the search for histiocytes and infectious agents.

### Blood screening for infectious diseases

Maternal blood and umbilical cord blood are being investigated for bacterial and eukaryotic agents (*Treponema pallidum, Chlamydia trachomatis, Streptococcus agalactiae* and *Toxoplasma gondii*), DNA virus (Parvovirus B19, Cytomegalovirus, Human Herpesvirus 6) using Real-Time PCR (RT-qPCR), as well for RNA virus (Dengue and Zika virus) using one-step RT-qPCR. All protocols are adapted from previous studies,[29–36] performed in a QuantStudio 6 Flex qPCR system equipment (Applied Biosystems, Thermo Fisher, USA) and analysed using Design and Analysis V.2.6 software (Applied Biosystems, Thermo Fisher, USA).

Serological tests are performed for IgM and IgG antibodies detection with commercial kits of ELISA for all viruses above mentioned, *T. gondii and C. trachomatis*. For Syphilis screening, Elisa and non-treponemal (Venereal disease research laboratory, VDRL) tests are used.

### Angiogenic factors detection

Laboratory blood tests are being conducted to evaluate vascular endothelial growth factor receptor 1 (sFlt-1) and placental growth factors (P1GF), according to Costa *et al*.[37] After blood collection in BD Vacutainer SST tubes (BD Ind. Cir.), the serum was separated, aliquoted and stored at −80°C until analysis. We assayed sFlt-1 and P1GF by ELISA test using Quantikine kits (R&D Systems, Minneapolis, Minnesota, USA), performed according to the manufacturer's instructions. The samples were run in duplicate by a single investigator blinded to the clinical outcomes. The minimum detectable doses are 3.5 pg/mL for sFlt-1 and 7.0 pg/mL for P1GF.

### Air pollution

Exposure to air pollution experienced by mothers of cases and controls are being evaluated using different approaches, through a geographical information system, based on the georeferencing of maternal addresses during pregnancy.

The first indicator is a direct measurement of the average concentration of pollutants from the 14 air quality monitoring stations of the São Paulo Environmental Company, which provides daily records of sulphur dioxide, particulate matter ($PM_{10}$ and $PM_{2.5}$), carbon monoxide, ozone and nitrogen dioxide. For each participant, the pollutant mean levels will be calculated in defined periods of

pregnancy (weeks, months or trimesters), from the monitoring station closest to the mother's residence, with the date of birth and gestational age as reference. In addition, gridded satellite estimates of monthly and daily mean levels of pollutants will be obtained and averaged for a buffer area around each residential address.

Indirect exposure indicators will also be considered the exposure to vehicle traffic, such as the distance from the mothers' residence to main traffic routes, especially those with the highest flow. This indicator combines data on the flow of vehicles and the distance from the roads around the mothers' homes, known as distance-weighted traffic density,[38] which assumes that the greater the vehicle flow around the residence, the greater the emission of pollutants, and greater exposure of residents.

Moreover, data on prenatal exposure to air pollution can be analysed with placental growth and function markers, which are biomarkers useful to assess the effect on endothelial changes. Data analysis may include exploring single-pollutant and multi-pollutant models, air quality levels as quartiles/quintiles, maternal exposure at work by estimating air pollution at work for those mothers who reported working in fixed locations other than their homes, and other associated risk factors, and comparing the observed levels with those proposed as safe thresholds by the Brazilian government and the WHO.

### Bereavement interviews with mothers of stillbirth

To assess the mother's bereavement after the stillbirth, home interviews are carried out in a subsample of 100 cases 1–2 months after hospital discharge to learn about the grieving experiences of participants and their families, feelings about the loss, return to daily and social activities, and support received from health services during and after hospitalisation. These interviews are being recorded and transcribed. A Portuguese version of the Perinatal Grief Scale[39] and a semistructured questionnaire are being applied.

### Interviews with hospital's and midwives' managers

Based on a semistructured questionnaire, hospitals' directors and midwives' coordinators from the participating municipal and state health services are being interviewed about the care provided to mothers who were admitted to the hospital with stillbirth or those who had a stillbirth in the hospital. Moreover, it was asked about their understanding of official care guidelines.

## Data analysis plan

The contribution of sociodemographic, biological, psychosocial, fetal health and environmental risk factors on stillbirth, as well as health services access and its use, will be evaluated by a set of models, including multivariate analyses such as logistic regression models and spatial regression with covariates. Causal models include the use of causal graphs (eg, directed acyclic graphs—DAGs) to systematically represent assumptions, known relationships and hypothesised relations[40]; structural equation models[41] will be used to test theory-driven conceptual models and spatial structural equation models[42] will include spatial correlations in structural equation models. Exploratory structural equations models will be used to identify cross-loads on the factors and advance understanding of the stillbirth causes in this population.[43] All these models access the role of variables as mediators, moderators, confounders and colliders, aiming to understand their interrelations starting from initial conceptual models. The data collection and storage flow are described in figure 2.

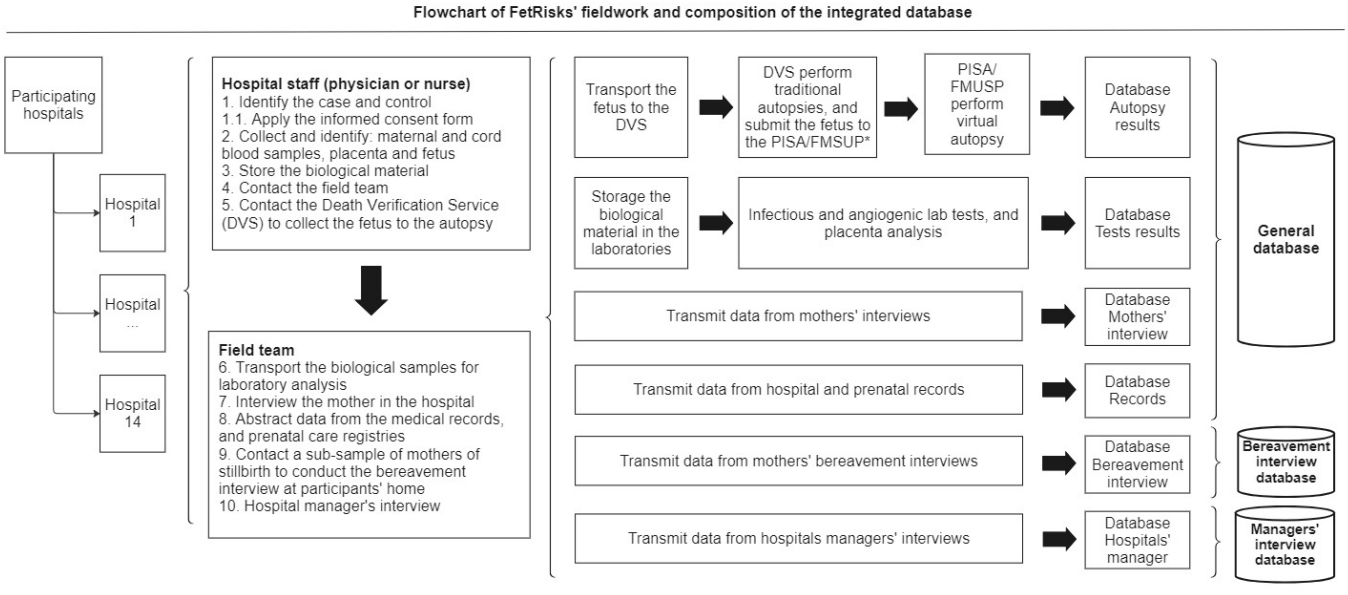


**Figure 2** General information flow of the FetRisks project. *PISA/FMUSP, Imaging Platform in the Autopsy Room of the Faculdade de Medicina, Universidade de Sao Paulo.

This study is made up of several subprojects that will examine different risk factors for stillbirths. Initially, we intend to carry out individual logistic regression analyses for each subproject: (a) traditional epidemiological risk factors for fetal death, including analysis of socioeconomic and demographic variables; (b) biological mechanisms, especially placental mechanisms; (c) maternal infections and (d) air pollution. We will use likelihood ratio tests for variable selection. Access to health services, prenatal care and childbirth will also be examined independently but will be considered as mediators of other risk factors for stillbirth. Possible effect modifiers will be examined by stratification. As we are collecting information from different instruments and sources, we will be checking similar variables for data accuracy and consistency.

The result of the subgroup analysis will be integrated into a hierarchical model, defining proximal and distal variables based on a proposed biological mechanism to be defined at that stage. For this, we will apply machine learning methods that have been developed for selecting features with greater predictive capacity, which includes penalised regressions, with the least absolute shrinkage and selection operator regularisation and to analyse the dependencies among characteristics, we will apply Bayesian networks. Moreover, DAGs will be used to select covariates for statistical adjustment, identify sources of bias and support causal interpretation.

The collected data will be analysed through the software R Studio, V.4.2.2 (Boston, Massachusetts, USA), and Stata, V.16 (StataCorps), while the geospatial information will be analysed through the QGis V.3.32.0 Lima (QGIS Association, 2023).

### FetRisks study's timeline

Hospitals were included and began data collection after ethics approval and had the terms of reference signed. Data collection started in December 2019 and was expected to last for 2 years, but it was suspended in 2020 due to the COVID-19 pandemic as the demand for health services was reduced, and some of the participating hospitals were destined for COVID-19 care. Thus, data collection was extended, and it is estimated to be finished by the end of 2023.

Other challenges encountered were the frequent change of managers at the participating hospitals and the high turnover of HCWs, requiring new agreements, recurrent training, awareness-raising meetings and guidance on the study aims and protocols, as well as training for data collection and analysis procedures. Data cleaning, processing and treatment are carried out constantly, and it is expected to last until the beginning of 2024. Composite variables are being created to facilitate data analysis, and exploratory analysis is being performed to understand the distribution of variables and the best statistical methods to consider all complex risk factors that may contribute to stillbirth. Potential local and international partners are being mapped, and partnerships are being established to support data interpretation. From 2024, a definitive statistical analysis will be conducted, and the results disseminated. Further approaches can be carried out, depending on financial and human resources availability.

### Patient and public involvement

Participants and the public were not involved in this study's planning or designing as its aims were primarily considered a priority of academia and decision-makers, considering stillbirth's impacts on public health and society. Even so, participants and the public were involved in reviewing the pilot survey and had a chance to comment on the clarity and utility of the research and addressed issues. Moreover, public agents and organisations related to maternal and child health will be contacted, and an open symposium is being planned to discuss with experts and the community the study's preliminary findings, their relevance and how to improve maternal and child health based on them. Thus, it is expected that the study's participants, policy-makers and related organisations help us to indicate the study's key findings and outputs to be disseminated to a broader audience.

### Participating institutions

This multidisciplinary project is being conducted by the Departamento de Medicina Preventiva, Departamento de Obstetrícia e Ginecologia, Departamento de Patologia and IMT of the FMUSP, Departamento de Epidemiologia of the Faculdade de Saúde Pública, Universidade de São Paulo and the London School of Hygiene & Tropical Medicine. Moreover, the participating hospitals are listed in table 1.

**Table 1** FetRisks participating hospitals, São Paulo, Brazil.

| | |
|---|---|
| Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) | Hospital Municipal Dr. Moysés Deutsch (M'Boi Mirim) |
| Hospital Universitário da Universidade de São Paulo (HU-USP) | Hospital Maternidade Leonor Mendes de Barros |
| Hospital Municipal Doutor Fernando Mauro Pires da Rocha—Campo Limpo | Hospital Municipal e Maternidade Prof. Mário Degni (Sarah) |
| Hospital Maternidade Vila Nova Cachoeirinha | Hospital Geral de São Mateus |
| Hospital Maternidade Interlagos | Hospital Geral de Pedreira |
| Hospital Municipal Prof. Dr. Waldomiro de Paula (Planalto) | Conjunto Hospitalar do Mandaqui |
| Hospital Municipal Cidade Tiradentes | Hospital Santa Marcelina de Itaquera |

### Potential study's limitations

We can anticipate some limitations of this study, such as difficulties in enrolling participants and obtaining responses soon after birth; recall bias mainly related to exposures (likely different for cases and controls); homogeneity of participants' characteristics since this study is conducted only in public hospitals; loss of medical records and lack of recording of clinical information. The study power might not permit significant estimations of risk for each individual study variable. To address these limitations, we only include mothers who volunteered to participate and who were emotionally stable to be interviewed; the questionnaires and interview guides have easy-to-understand language and interviewers were trained so that the way data is collected does not influence the participants' responses; we included hospitals from different regions of the city with the aim of greater representation; and we are collecting data from several instruments both to check the consistency of the information and to fill in any missing information in one of the instruments.

## ETHICS AND RESULTS DISSEMINATION

Hospital managers were contacted to include the hospital in the study, receive information about the study's aims and methodology, request support for data collection, clarify doubts about the project, etc. Hospitals that agreed to participate were incorporated into the study after approval of their respective ethics committees. Thus, this study was approved by the Ethics Committee of the Municipal Health Secretary (process nº 16509319.0.3012.5551) and of the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo HCFMUSP (process nº 16509319.0.0000.0068). Participants' information is collected after learning about the research aims and risks, and providing informed written consent. All identifiable information is kept confidential.

This study results will be communicated to the study participants and policy-makers through individual and collective meetings, and to the scientific community through conferences presentation and manuscripts published in international peer-reviewed journals. All anonymised data will be analysed by the University of São Paulo and afterward can be made available in data depositories or on request.

The FetRisks study may allow the analysis of stillbirth and its risk factors in a multidisciplinary and integrated approach, especially those related to socioeconomic characteristics, maternal biological factors, maternal and fetal outcomes, environmental exposures, hospital care, and prenatal care access and quality. It may also enable to explore of new statistical methods applied to the multicausal aetiological mapping of stillbirth and examine the context of stillbirth for mothers and families, as well as the support offered by the health services to grieving families.

Lastly, from the identification and measurement of risk factors of stillbirth, it can be possible to quantify their relative contribution and to determine the fraction attributable to the studied population. Thus, it may provide subsidies for the development and improvement of public policies and protocols for prenatal and childbirth care for health systems, particularly for the SUS, aimed at preventing stillbirth, improving pregnant and perinatal healthcare, and supporting for bereaved families after stillbirth.

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