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Cohort Profile: The Pregnancy Research on Inflammation, Nutrition, & City Environment: Systematic Analyses Study (PRINCESA) Cohort, 2009–2015

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Author Contributions

All authors contributed to this paper. Data collection was performed by Marisol Castillo-Castrejon, Myrna Godines-Enriquez, Vanesa Morales-Hernández, Lilia Monroy-Ramírez de Arellano, and Felipe Vadillo-Ortega; data processing and analysis were performed by Miatta Buxton, Marisol Castillo-Castrejon, Brisa N. Sanchez, Alvaro Osornio-Vargas, Mislael Valentin-Cortes, and Marie S. O'Neill. The first draft of the manuscript was written by Miatta Buxton and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and material

The PRINCESA investigators invite interested researchers to email Dr. Marie O'Neill, at marieo@umich.edu and Dr. Felipe Vadillo-Ortega at fvadillo@inmegen.gob.mx for information regarding collaboration.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This study was performed in line with the ethical principles and guidelines for the protection of human subjects of research outlined in the Belmont Report. The PRINCESA study was approved by the institutional review board from the University of Michigan, Ann Arbor and the ethics committees at the Hospital Materno Infantil Inguaran and the National Autonomous University of Mexico, Mexico City. The Institutional Review Board approval number for the project is HUM00023514.

Consent to participate

Details of the study, including purpose, expected duration, potential risks and benefits, and procedures were provided to eligible participants, who were then invited to ask questions about the study. Subsequently, written consent was obtained from all individual participants included in the study.

Abstract

The Pregnancy Research on Inflammation, Nutrition, & City Environment: Systematic Analyses Study (PRINCESA) cohort was set up to evaluate associations between air pollution and birth outcomes among pregnant persons in Mexico City. Specifically, the study was designed to improve air pollution exposure assessment and elucidate biological mechanisms underlying associations between maternal exposures and adverse pregnancy outcomes. Pregnant persons (all women) (N=935) between ages 18 – 45 who lived and/or worked in metropolitan Mexico City, Mexico, from 2009–2015 and liveborn singleton infants (N=815) of participants who completed follow-up were enrolled in the cohort. We followed participants monthly from enrollment to delivery and the following categories of data were obtained: demographic, medical and obstetric history, geo-referenced data, repeated measures on daily activity patterns, reported food intake, anthropometric, clinical and obstetric data, 20 serum and 20 cervicovaginal cytokines, and lower reproductive tract infection. Repeated ultrasound measures of fetal parameters and infant birth data are also included in the study's database. In addition, PRINCESA investigators calculated air pollution exposure measures for six pollutants measured by the Mexico City Atmospheric Monitoring System (SIMAT). These estimates utilize participants' addresses to account for spatial variation in exposure (nearest monitor, inverse distance weighting, and kriging) and are available daily during pregnancy for participants. To date, associations between environmental and nutritional impacts on maternal and child health outcomes have been evaluated. PRINCESA has a comprehensive database of maternal and infant data and biological samples and offers collaboration opportunities to study associations between environmental and other factors, including nutrition and pregnancy outcomes.

Keywords

Cohort; longitudinal; pregnancy outcome; maternal exposure; air pollution

Introduction

Adverse pregnancy outcomes can affect both mother and offspring and result in long-term morbidity and mortality.[1] In 2015, the adverse pregnancy outcomes of preterm birth and low birth weight combined were the second leading cause of infant mortality in the United States.[2] Specifically, preterm birth is an international public health problem [3] and global estimates indicate that rates are increasing [4] despite research [5] and prevention efforts.[6] Air pollution has been identified as a potentially important risk factor for adverse pregnancy outcomes due to ubiquitous exposure. Air pollution's association with preterm birth is hypothesized to occur via an inflammatory pathway, which may result from either inflammation produced in the lungs and subsequently disseminated to other parts of the body or by the transport of fine pollutant particles to other part of the body, including the placenta.[7] Additionally, inadequate nutrition is reported to be an additional risk factor for adverse pregnancy outcomes.[8] In addition to its independent association with adverse pregnancy outcomes, nutrition plays an important role as it could modify the association between air pollution and adverse pregnancy outcomes.[9]

Even after air pollution's identification as a potential risk factor for adverse pregnancy outcomes, knowledge gaps persisted due to the limitations of previous studies. Prior to 2007, most studies evaluating the effects of air pollution on pregnancy outcomes utilized data from birth registries or other existing datasets that lacked important individual-level data needed to control for confounders [10] and the pertinent human samples required to elucidate the postulated biological mechanisms and pathways.[11] In addition, exposure assessment methods have had limitations in studies which estimate air pollution using citywide averages or exposure estimates derived from a single monitor, not accounting for participants' distance from monitors. Some research has utilized estimates of exposure to fine particles, combining satellite imagery modeled along with ground monitor data and this has enabled important work with finer scale exposure resolution.[12] Data on work location and environment, as well as daily indoor/outdoor mobility patterns, which are not captured with the modeled exposures, may improve existing exposure assessment methods.

These limitations were discussed at an International Workshop on 'Air Pollution and Human Reproduction' and subsequently highlighted in a published report, and they remain a concern in this field.[13] In addition, in a separate meeting of experts, the U.S. Institute of Medicine highlighted the complex nature of studying preterm birth. They emphasized a need for research to improve understanding of the causes of preterm birth, evaluate multiple risk factors simultaneously, and investigate factors that promote disparities in preterm birth rates.[14]

Scope of research

The Pregnancy Research on Inflammation, Nutrition, and City Environment: Systematic Analyses (PRINCESA) Study was established in response to the needs highlighted by the Institute of Medicine and International Workshop reports. The PRINCESA study incorporates findings and recommendations from the previous meetings to address limitations identified in the literature. It was designed to address the following research questions: 1) to evaluate the association between the following six air pollutants: particulate matter less than ten (PM_{10}) and 2.5 ($PM_{2.5}$) microns in aerodynamic diameter; carbon monoxide (CO); nitrogen dioxide (NO_2); ozone (O_3); sulfur dioxide (SO_2); and preterm birth; 2) to evaluate if monthly air pollution exposure is associated with pro- and anti-inflammatory cytokines obtained from cervicovaginal samples collected at monthly prenatal visits; and 3) to evaluate the composition of $PM_{2.5}$ and PM_{10} particles obtained from five locations in the Mexico City Metropolitan area.

The study was funded by grants from the National Institute of Environmental Health Sciences [grant numbers: R01 ES016932 and R01 ES017022], the Mexican National Council on Science and Technology (CONACYT), and the University of Michigan. The PRINCESA study was approved by the institutional review board from the University of Michigan, Ann Arbor, and the ethics committees at the Secretaría de Salud del Gobierno de la Ciudad de México and the National Autonomous University of Mexico, Mexico City.

Study design

Overview

The PRINCESA study is a longitudinal study of 935 participants pregnant with singleton fetuses at enrollment. Pregnant women were enrolled between 2009 and 2014 for subsequent to follow up during the duration of their pregnancies between 2009 – 2015. Interested individuals were screened to determine eligibility at the Hospital Materno Infantil Inguarán, the primary location where participants received prenatal care, and thus used for enrollment and follow-up. The study was conducted in Mexico City, a metropolis[15] with unique geographical features and commercial and industrial activities that contribute to high levels of air pollution. [16] The Mexico City government, which started collecting air pollution data in 1986, has an extensive system of air pollution monitors and this serves as the source of air pollution data used in the PRINCESA cohort. by.[17] Additionally, the PRINCESA study was initiated in conjunction with a toxicological study which evaluated *in vitro* responses among cells exposed to Mexico City particulate air pollution collected from five locations representing regions where cohort participants resided.

Eligibility and enrollment

Individuals were eligible to participate in the study if they lived and worked in the Mexico City Metropolitan Area (Mexico City and surrounding areas), were 18 or older, carried a singleton, had an ultrasound, lacked medical or obstetric complications at enrollment, and could attend monthly prenatal visits. In addition, the original inclusion criteria considered that participants were non-smokers and less than 18 weeks pregnant at enrollment. However, the study was amended to include a small number of smokers (n=15) and persons with gestational age beyond 18 weeks of gestation at enrollment (n=41). Table 1 shows the baseline characteristics of participants in the PRINCESA cohort.

The administration of study questionnaires, physical and ultrasound exams, and collection of samples occurred approximately every month. The one exception was the on-site determination of global positioning system (GPS) coordinates from participants' residences and work locations using a Garmin device; each set of coordinates was collected once during the course of the study. For a few participants whose coordinates were not collected, Google Earth was used along with the residential address to determine coordinates. Although information regarding an address change was collected for participants who moved during the study, the second set of GPS coordinates was not collected for these participants, but the move was noted in the record.

Visit stages

Pregnant patients attending the Hospital Materno Infantil Inguarán in Mexico City and those referred from local SEDESA clinics were invited to participate in the PRINCESA Study. First, participants were screened to evaluate enrollment eligibility. Screening data are available on all enrolled participants and include information on the length of time participants had lived and/or worked in Mexico City at the time of screening. In addition, the Mexico City metropolitan area was divided into five regions defined around the five monitoring stations where air pollution samples were collected for toxicologic research

[18] using Thiessen polygons. The point representing each monitoring site is a polygon centroid, and the polygon boundary circumscribes the area closest to the given monitor. These zones defined the study area participants' recruiting regions, enhancing the spatial pollution exposure contrast. They also allowed the evaluation of regional concordance between epidemiologic and toxicologic results. Participants identified the zone(s) that included their residence and/or work location. Demographic, behavioral clinical data and biological samples were collected at the first visit, follow up visits and at birth. Figure 1 describes the data collection process utilized in the study.

Data collected in this study—A clinical team for prenatal care comprised a certified obstetrics and gynecology specialist who was also certified in fetal medicine, a nutritionist and a nurse who both specialized in perinatal care and they led the study's data collection. The PRINCESA study used standardized clinical protocols and has data in the following categories: questionnaire, clinical, biological, infant parameters (birthweight, gestational age, ultrasound scans), residential longitude and latitude coordinates, and estimated air pollution exposures. Table 2 summarizes the types and frequency of data collected. Questionnaires were administered to collect demographic, medical history, obstetric history, nutritional status (anthropometry, biochemical biomarkers, clinical follow-up, dietary intake information), fetal growth and development, and time activity; information on exposure to secondhand smoke was also obtained.

Time activity questionnaires were administered to collect information on participants' activities to inform the air pollution exposure assessment methods. A weekend form was completed at home after the in-clinic visit (also once a month) to account for routine weekend activities. Finally, food frequency questionnaires (reference period: a month before the visit) and 24-hour dietary recall (day prior to the visit) were alternatingly administered to document participants' food consumption prior to the visit. Food frequency questionnaires and 24-hour dietary recall were administered by trained interviewers (pen and paper format).

Cervicovaginal swab samples were collected at each visit for microbiology analysis and quantifying 20 cytokines. Peripheral blood samples were collected during each visit to quantify the same 20 cytokines from cervicovaginal samples. Cytokines quantified from both cervicovaginal and blood samples were: Eotaxin, Interferon-gamma (IFNγ), interleukin-10 (IL-10), IL-12p40, IL-12p70, IL-17, IL-1rα, soluble IL-2 receptor alpha (sIL-2rα), IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, Interferon-gamma inducible protein (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1α), macrophage inflammatory protein-1 beta (MIP-1β), TNFα, and vascular endothelial growth factor (VEGF). Additionally, urine samples were collected for general urine tests to determine cotinine levels to evaluate participants' exposure to secondhand smoke and assess infection in symptomatic patients.

Data were generated on the following fetal growth and development parameters: biparietal diameter (BPD), humerus length (HL), head circumference (HC), femur length (FL), amniotic fluid index, fetal weight (FW), gestational age (UGA). These measures were obtained by ultrasound performed by three trained study clinicians who were evaluated for interrater agreement during the study, which was determined to be very good (unpublished

data) and reviewed by a fetal medicine specialist. Infant data, including gestational age and weight at birth, were collected to characterize birth outcomes.

Air Pollution Data

The PRINCESA study utilizes air pollution data collected and processed on an ongoing basis by the Sistema de Monitoreo Atmosférico de la Ciudad de México (SIMAT). (http://ghdx.healthdata.org/record/mexico-mexico-city-automatic-air-quality-monitoring-network-database) SIMAT collects hourly air pollution data on the following pollutants: carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), particulate matter less than ten microns in aerodynamic diameter (PM) - PM_{10}, $PM_{2.5}$, and sulfur dioxide (SO_2); the fine-scale data available allowed for computation of a range of exposure periods of interest. Moreover, the cohort has daily pregnancy-wide air pollution estimates constructed using four methods, including three that account for residence location. The methods used to estimate air pollution levels are ordinary kriging, citywide averaging, inverse distance weighting and nearest monitor.[19] Ordinary kriging, inverse distance weighting and nearest monitor incorporated information on participants' residence, but citywide averaging did not include information about where participants lived. In addition, ordinary kriging and inverse distance weighting utilize modelling to estimate participants' exposure, whereas nearest monitor estimation uses air pollution concentrations from the monitor nearest to each participant's address.[19] Table 3 shows select percentiles across all three trimesters and overall pregnancy for ozone using the 4 air pollution estimation levels. The table illustrates the high levels of air pollution in Mexico City, with most women experiencing levels exceeding health-based guidelines. Similar types of data, which allow for evaluating several exposure periods, are available for the other five pollutants (not reported in this manuscript).

Estimation of gestational age

Gestational age estimates were generated for PRINCESA participants based on ultrasound and/or the last menstrual period (LMP) reported during screening in most cases. However, the first visit report was used for a limited number of participants. Differences in the estimation of gestational age resulted for a subset of participants. Sample sizes for preterm birth status based on the gestational age estimation method and other pregnancy outcomes for the cohort are shown in Table 4. To create a comprehensive sample, we reconciled differences between ultrasound and LMP using recommendations by the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice.[20] The recommendations provide guidelines for making decisions about re-dating gestational age based on gestational age estimated by LMP at the time of ultrasonography and the difference in gestational age (in the number of days) between LMP and ultrasound dating. Decisions made about the gestational age dating method selected are presented in Table S1.

Figure 2 is a flow chart of the outcomes for all originally recruited PRINCESA participants.

Results

At enrollment, most of the participants in the PRINCESA Cohort were between the ages of 18 and 34; 18–24 (53.5%) and 25–34 (36.8 %). The cohort included 4.3%, 45.4%, 32.8% and 17.4% of participants who were classified as underweight, normal weight, overweight or obese, respectively, prior to becoming pregnant. Enrollment of participants in the cohort mostly occurred during the first (40%) and second trimester (57.3%) of pregnancy. In addition, secondary education was the most common level of education completed at 39.7 % followed by vocational/technical education at 30.2%. More than half of participants (51%) reported living together, but were not married to their partner, 25.5% were single and 22.3 % of participants were married. Although few participants reported smoking during pregnancy as this was initially an exclusion criterion, 41.8% reported that they were exposed to secondhand smoke at home, while 42.6% reported they were not exposed to secondhand smoke and 63.5% of participants had a personal history of smoking prior pregnancy. The distribution of infant sex was 48.1% and 50.8” for males and females, respectively.

There were eight follow up stages and the percent completed by participants for each visit ranged from 89.7% for follow up visit stage 1 to 0.1% for follow up visit stage 8. The number of follow up visits completed differed across participants due to varying gestational ages at enrollment, length of gestation and overall compliance with the study protocol.

Although different methods were used to generate air pollution estimates, the trimester-specific and overall pregnancy percentiles of daily 8-hour maximum ozone varied slightly across methods, with the largest variation occurring between citywide average and ordinary kriging during first trimester and overall pregnancy.

In addition, data from the PRINCESA cohort have been used to evaluate important research questions related to maternal health and environmental impacts on maternal and child health outcomes. Table 5 includes key findings from PRINCESA publications to date, including complementary *in vitro* publications.

What are the main strengths and weaknesses?

A main strength of the PRINCESA study is that it innovatively addresses the limitations of previous studies by using an interdisciplinary approach to understand the complex relationships between air pollution and adverse pregnancy outcomes. In addition, this study recruited its target sample size and collected individual-level data every month, unlike birth registry datasets that, although often very large, usually lack information to control for important confounders. Specifically, the longitudinal design led to monthly and multiple measures of a survey, clinical, dietary, anthropometric, and cytokine data, a characteristic that is not common in most longitudinal studies of air pollution and other environmental exposures and adverse pregnancy outcomes.

In addition, this study has daily air pollution estimates for six air pollutants matched to the pregnancy period for each participant. Moreover, the 20 cytokines quantified from simultaneously collected cervicovaginal and serum samples provide an opportunity to understand the potential biological mechanisms involved in the association between air

pollution and the adverse impact on human pregnancy. Furthermore, repeated ultrasound measures of four fetal parameters to measure fetal growth during pregnancy is also a strength of this study. The availability of such data allows for comparisons with birthweight and determining windows of susceptibility to various air pollutants, and understanding which periods of restricted intrauterine growth (IUGR) are associated with adverse birth outcomes. However, the study has some limitations. The study has few data points early in pregnancy because most participants were enrolled in the third month. This limits our ability to understand how exposure to air pollution during and shortly after conception affects early processes in pregnancy and how those effects may later contribute to other processes during the course of pregnancy. Another limitation is that birth data such as birthweight and biological samples for some participants in the study were not collected due to delivery at other hospitals. Therefore, the sample size varies depending on the study question and the variables utilized. Although enrolling an approximately similar number of participants from a diverse geographic spread of Mexico City (divided into five zones for this study) was a part of the study's recruitment strategy, a majority of recruited participants lived in areas surrounding the Hospital Materno Infantil Inguarán. This geographic clustering of participants may limit a comprehensive evaluation of potential differences in environmental impact by zone.

Future directions

The PRINCESA study team continues to work to evaluate research questions related to air pollution exposure and pregnancy outcomes in this cohort. We are also working to utilize the reported intake of foods and supplements to calculate and describe a measure of dietary antioxidant intake during pregnancy and to evaluate associations of antioxidant intake during gestation and exposure to fine particulate air pollution ($PM_{2.5}$) during select gestational periods with preterm delivery. Additionally, we are characterizing other area-level environmental exposures, including green space and food establishments, to link to outcomes in this cohort. The work mentioned above will lead to additional data types, including a summary measure of antioxidant intake and new exposure metrics, which will be available to PRINCESA participants.

We welcome opportunities for conducting pooled and harmonized analysis with other pregnancy cohorts with data to address various hypotheses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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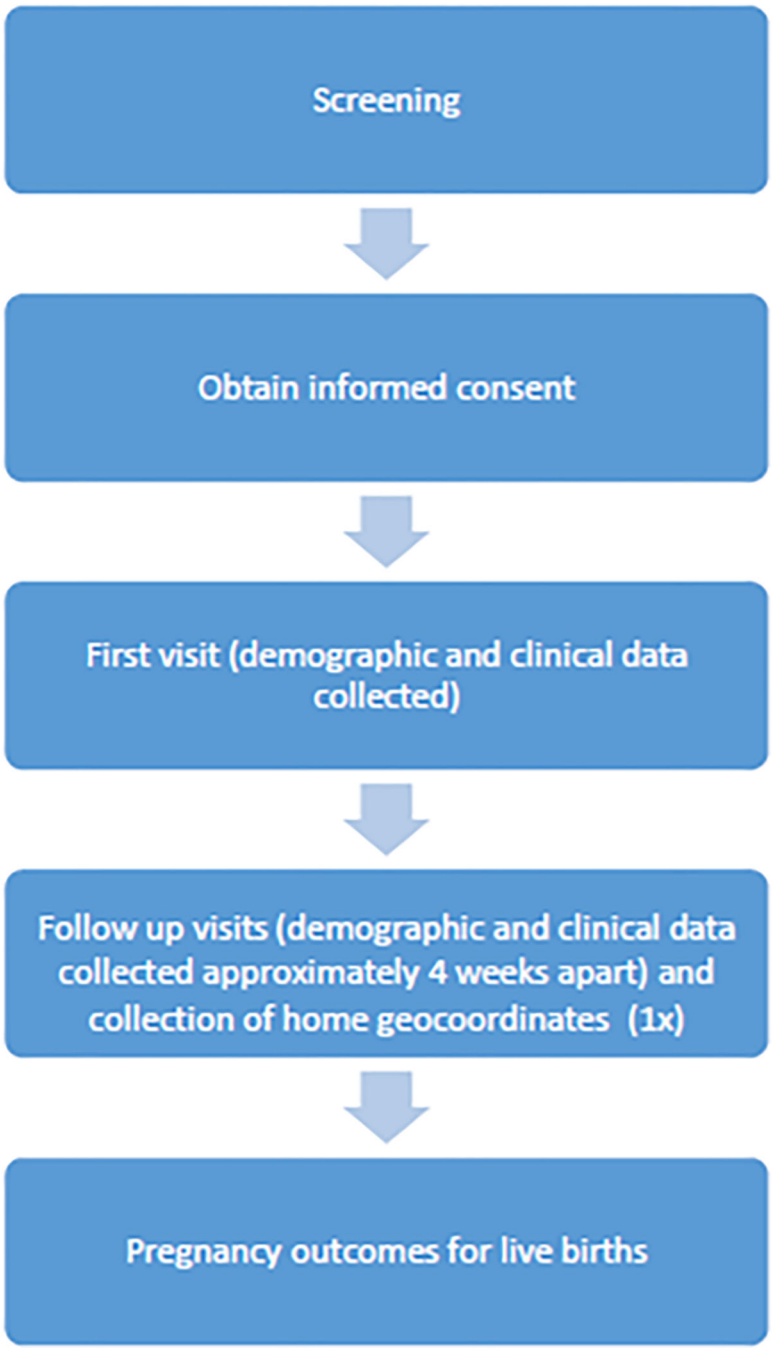

Figure 1.
Flow diagram of data collection stages, PRINCESA Cohort, 2009 – 2015

Summary of Birth Characteristics among Participants in the PRINCESA Cohort, N = 935			
Gestational Age (GA) Categories			
GA ≥ 37 weeks	**GA ≥ 20 and < 37 weeks**	**GA < 20 weeks**	**Unknown GA n=97**
Live Birth n=732	Live Birth n=79 Stillborn n=6	Stillborn n=19 Missing n=2	Live Birth[1] n=4 Stillborn[1] n=1 Missing[2] n=92
Delivery Type			
Vaginal n= 479	C-Section n=294	Induced n=27	Unknown n=135
Gender			
Male n=392	Female n=414	Unknown n=129	
Birthweight in Grams (g)			
1880 - 4700g n=721	**605 - 3515g** n=76	**100 - 270g**[3] n=2	**2820 - 3860g** n=4

[1] Live birth information without LMP available n=4

[2] Voluntary withdrawal n= 42, Moved out of study area n= 9, Medical reason n=17, Missing n= 21, reasons n= 3

[3] Miscarriage

Figure 2.

Flow Diagram of Outcomes among Participants in the PRINCESA Cohort, 2009–2015, N = 935

Table 1.

Baseline and birth characteristics of the PRINCESA Cohort participants, 2009 – 2015

Maternal Characteristics	N (%)
Age at enrollment (years)	
18–24	500 (53.5)
25–34	344 (36.8)
≥35	91 (9.7)
Pre-pregnancy BMI (kg/m^2)	
<18.5	40 (4.3)
18.5–24.9	424 (45.4)
25–29.9	307 (32.8)
≥30	163 (17.4)
Missing	1 (0.1)
Gestational age at enrollment (weeks)	
≤ 13	374 (40.0)
14 – 26	536 (57.3)
> 26	1 (0.1)
Missing	24 (2.6)
Education	
Primary or no schooling	88 (9.4)
Secondary	371 (39.7)
Vocational/ Technical	282 (30.2)
Associate or higher	70 (7.5)
Missing	124 (13.3)
Marital Status	
Single	238 (25.5)
Married	208 (22.3)
Widowed/divorced	7 (0.8)
Living together but not married	477 (51.0)
Missing	5 (0.5)
Parity	
0	324 (34.7)
1–2	392 (41.9)
≥ 3	52 (5.6)
Missing	167 (17.9)
History of smoking	
Yes	594 (63.5)
No	332 (35.5)
Missing	9 (1.0)
Secondhand smoke exposure (at home)	
Yes	391 (41.8)
No	398 (42.6)

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Maternal Characteristics	**N (%)**
Missing	146 (15.6)
Child Characteristics among 815 live births	
Infant Sex	
Male	392 (48.1)
Female	414 (50.8)
Missing	9 (1.1)

Table 2.

Summary of the data measured in the PRINCESA Cohort, 2009 – 2015

Data type	Enrollment	Follow up visits	Birth
Questionnaire data			
Demographic	✓	✓	
Obstetric history (previous and current pregnancy)	✓	✓	
Medical history (prior to and during pregnancy)	✓	✓	
Nutritional status history	✓	✓	
Time activity data (TAD) - weekday and weekend	✓	✓	
Exposure to cigarette smoke	✓	✓ (TAD)	
24-hour recall and food frequency questionnaire	✓	✓	
Clinical data			
Anthropometric measures	✓	✓	
Nutritional status	✓	✓	
Fetal growth and development	✓	✓	
Medical and obstetric data	✓	✓	
Biological samples			
Cervico-vaginal exudates (cytokines and infection)	✓	✓	
Blood (serum cytokines)	✓	✓	
Urine (cotinine and infection)	✓	✓	
Fetus/Infant data			
Ultrasound measures of fetal parameters Birth weight, date, cord blood (subset)	✓	✓	
Birth weight, date, cord blood (subset)			✓
Coordinates (GPS)			
Residence		Once during follow up	
Work		Once during follow up	
Daily during pregnancy air pollution exposure estimates for CO, NO_2, O_3, SO_2 $PM_{2.5}$, PM_{10}			
City-wide average for all reporting monitors			
Inverse distance weighting			
Geostatistical kriging			
Nearest monitor			

Table 3.

Trimester-specific and overall pregnancy percentiles of daily 8-hour maximum ozone (ppb) estimate by exposure assessment method for participants in the PRINCESA Cohort, 2009 – 2015. World Health Organization guideline for ozone, peak season 8-hour maximum, is 100 ug/m3, approximately 51 pbb. (https://www.who.int/publications/i/item/9789240034228)

Exposure Assessment Method	Mean (SD)	Percentiles of exposure distribution by trimester					
		5th	25th	50th	75th	95th	Max
First Trimester							
CWA	58.5 (8.9)	46.3	51.7	56.2	64.6	74.4	90.2
NM	55.5 (9.2)	42.9	48.8	53.5	61.4	72.5	90.1
IDW	56.4 (9.0)	43.6	49.8	54.1	62.6	73.2	89.0
KG	55.7 (8.8)	43.9	49.4	53.8	60.2	73.5	97.5
Second Trimester							
CWA	59.0 (9.3)	46.3	51.4	56.9	65.8	77.0	82.2
NM	56.1 (9.3)	43.1	49.2	54.1	62.9	72.6	80.7
IDW	57.0 (9.2)	44.3	50.2	54.8	63.9	73.7	81.2
KG	56.2 (9.0)	44.0	49.8	54.2	62.3	73.1	79.5
Third Trimester							
CWA	56.7 (8.2)	46.8	50.6	54.9	60.9	73.1	84.7
NM	54.2 (8.4)	43.6	48.3	52.2	58.1	70.8	80.5
IDW	54.9 (8.2)	44.6	49.1	52.8	58.7	71.7	81.5
KG	54.3 (7.7)	45.0	49.0	52.7	57.4	70.7	80.2
Overall Pregnancy							
CWA	58.0 (4.1)	52.0	55.4	57.3	61.0	64.2	90.2
NM	55.3 (4.3)	49.0	52.2	55.3	58.6	61.0	90.1
IDW	56.1 (4.1)	50.2	53.2	55.9	59.1	61.8	89.0
KG	55.0 (3.9)	50.0	52.2	55.0	57.6	60.6	97.5

CWA=Citywide average; NM=Nearest Monitor; IDW=Inverse Distance Weighting; KG=Kriging

Table 4.

Outcomes of singleton fetuses at birth in the PRINCESA Cohort, 2009 – 2015

Outcomes	N (%)
All Births	
Birth status	
Live birth	815 (96.9)
Stillbirth/Miscarriage	26 (3.1)
Live Births	
Preterm birth status (LMP estimate)	
Term	712 (87.4)
Preterm	86 (10.6)
Missing LMP	17 (2.1)
Preterm birth status (Ultrasound estimate)	
Term	651 (79.9)
Preterm	72 (8.8)
Missing Ultrasound	92 (11.3)
Preterm birth status (LMP complemented by Ultrasound)	
Term	732 (89.8)
Preterm	79 (9.7)
Missing	4 (0.5)
Birth weight (grams)	
< 2500	78 (9.6)
2500 – 4000	711 (87.2)
> 4000	10 (1.2)
Missing	16 (2.0)

Table 5:

Summary of findings from publications using data from the PRINCESA Cohort

Reference	Category	Research questions	Findings
Buxton et al, (IJERPH, 2021) [21]	Inflammation during pregnancy	We examined the effects of trimester timing on associations between 16 cervicovaginal cytokines (Eotaxin, IL-10, IL-12p40, IL-17, IL-1RA, sIL-2r, IL-1a, IL-1, IL-2, IL-6, IP-10, MCP-1, MIP-1, MIP-1, TNF, and VEGF) and preterm birth among 90 women throughout pregnancy.	We found significant positive associations between cytokines and preterm birth across trimesters. First-trimester cytokines had the strongest positive associations with preterm birth and second and third-semester associations were weaker but largely positively associated, except in the case of IL-1.
Buxton et al, (Am J (Perinatol, 2019) [22]	Inflammation during pregnancy	We characterized trajectories and concentrations of 20 cervicovaginal cytokines during pregnancy among women who delivered at term.	Mean concentrations of cervicovaginal cytokines were high yet stable among term pregnancies.
Ancira-Moreno, et al (Matern Child Nutr, 2020)[23]	Maternal diet	We evaluated the association between maternal diet quality and low birth weight in 660 pregnant participants using previous-day dietary intake reported at multiple prenatal visits. Diet was assessed using a priori (Maternal Diet Quality Score (MDQS)), and a posteriori (dietary patterns extracted by factor analysis) approaches.	Adherence to recommended dietary guidelines (higher MDQS) was associated with a reduced risk of low birth weight (odds ratio (OR): 0.22, 95% confidence interval (CI): 0.06, 0.75) compared with the lowest adherence category (reference group); by contrast, dietary patterns were not associated with low birth weight risk.
Ancira-Moreno, et al, (Nutrition, 2019)[24]	Maternal diet	We characterized gestational weight gain trajectories, (2) assessed associations of maternal dietary quality scores with gestational weight gain during early-mid pregnancy, middle pregnancy, late pregnancy, and prolonged pregnancy, and (3) evaluated the association between MDQS and adequacy of gestational weight gain throughout pregnancy.	Women with a pre-pregnancy body mass index (BMI) of ≥30 kg/m^2 had a slower rate of gestational weight gain than other BMI categories. Higher adherence to maternal dietary quality recommendations was protective against both inadequate and excessive gestational weight gain throughout pregnancy. Associations between diet and gestational weight gain differed by gestational period. Higher adherence to MDQS was associated with slower weight gain in the middle and prolonged late pregnancy, with a faster gestational weight gain in early and late pregnancy.
Buxton et al, (Science of The Total Environment, 2019)[25]	Air pollution and inflammation	We evaluated associations between air pollution and immunologic responses in the systemic circulation and lower reproductive tract and whether the systemic and reproductive tract immunologic responses were similar.	Median cervicovaginal levels of IL-6, Eotaxin, IP-10, MCP-1, MIP-1α, MIP-1β, and TNFα were higher than corresponding serum cytokines, significantly for IL-6 and IP-10. Cervico-vaginal and serum cytokines were not correlated, but cytokines from the same fluid were correlated. PM_{10} was positively associated with serum cytokines IL-6, IP-10, MIP-1β and Eotaxin but inversely associated with cervicovaginal TNF-alpha, IP-10, MIP-1β, MCP-1 and Eotaxin. CO was inversely associated with cervicovaginal TNF-alpha, IL-6, MIP-1β, MCP-1 and Eotaxin.
Manzano-León et al, (Environ Health Perspect, 2016) [26]	Air pollution and inflammation	We assessed seasonality in particulate matter composition and in vitro PM pro-inflammatory potential using multiple PM samples obtained during the rainy-warm and dry-cold seasons in five urban areas with different pollution sources. We tested the potential of the PM to induce TNF- alpha and IL- 6 secretion in cultured human monocytes, and we modeled pro- inflammatory responses using component scores.	Findings suggest that PM varied by size and season; particularly, soil-related constituents and combustion-related constituents varied by season. Elevated levels of cytokine production were associated with PM_{10} and component score C2 in the rainy-warm season. In contrast, reduced cytokine levels were associated with $PM_{2.5}$ and component score C1 in the dry-cold season.
Manzano-León et al, (J Biochem Mol Toxicol, 2013)[18]	Air pollution and inflammation	We assessed spatial variability in PM_{10} and $PM_{2.5}$ chemical composition and toxic effects using multiple PM samples collected during four months at five different sites in Mexico City. We measured toxicological responses in two cell lines (human THP-1 and murine	We found regional differences in PM composition between samples collected in residential and industrial areas. PM from residential areas had the most extensive mass explained by the elements studied compared to industrial areas that were richest in polycyclic aromatic hydrocarbons (PAHs). Exposing J774A.1 and THP-1 to PM caused the secretion of inflammatory cytokines,

Reference	Category	Research questions	Findings
		J774A.1) to assess their comparability in TNFα and IL-6 secretion.	which varied by sampling site and PM size, and PM_{10} produced more marked responses than $PM_{2.5}$.
Smarr et al, (Curr Opin Pediatr, 2013)[27]	Air pollution and fetal growth	We conducted a literature review to examine the available epidemiologic literature addressing maternal exposure to air pollutants and fetal growth during gestation assessed by ultrasound measurements.	We found six studies published at the time, which found that exposure to ambient air pollutants during pregnancy was inversely associated with growth rates and average attained the size of fetal parameters belonging to the growth profile. The available literature suggested that mean changes in head circumference, abdominal circumference, femur length, and biparietal diameter are negatively associated with early-pregnancy exposures to ambient and vehicle-related air pollution.