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Associations of Air Pollution and Hypertensive Disorders in Pregnancy

by

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Dedication

This dissertation is dedicated to my Kalita and Bhuyan family for their unconditional support.

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LIST OF ABBREVIATIONS

ACOG	American Colleges of Obstetrics and Gynecology
AHA	American Heart Association
ALT	Alanine Transaminase
ANS	Automatic Nervous System
AST	Aspartate Transaminase
BMI	Body mass index
Bpm	Beats Per Minute
CVS	Cardiovascular
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
DOHaD	Developmental Origin of Health and Disease
E	Eclampsia
HER	Electronic Health Record
EPA	Environment Protection Agency
GEOS-Chem	Goddard Earth Observing System (GEOS) of Chemicals
KPSC	Southern California Kaiser Permanente
LDH	Lactate Dehydrogenase
HELLP	Hemolysis, Elevated Liver Enzymes and Low platelet count syndrome
HR	Hazard Ratio
HDP	Hypertensive Disorders in Pregnancy

ICD-9	International Classification of Disease 9th revision
ICD-10	International Classification of Disease 10th revision
IL-6	Interleukin-6
IQR	Inter Quartile Range
OR	Odds ratio
PIH	Pregnancy Induced Hypertension
$PM_{2.5}$	PM with an aerodynamic diameter <2.5
PM_{10}	PM with an aerodynamic diameter <10
PNS	Parasympathetic Nervous System
ROS	Reactive Oxygen Species
SNS	Sympathetic Nervous System
SGA	Small for Gestational Age
TNF-∝	Tumor Necrosis Factor-∝
WHO	World Health Organization

ABSTRACT OF THE THESIS

Association Between Air Pollution and Hypertensive Disorders in Pregnancy

By

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University of California, Irvine 2022

Professor Jun Wu, Chair

Hypertensive disorders in pregnancy (HDP) are a leading cause of maternal and fetal morbidity and mortality world-wide. According to a recent CDC report, HDP have increased by 3% in 2019, implicating an association with environmental etiology. There are numerous reports of adverse health effects caused by fine particulate matter ($PM_{2.5}$), particularly on respiratory and cardiovascular health; however, their effects on changed CVS dynamic during pregnancy and associated HDP is unclear yet. Basic pathophysiology of HDP is largely unknown as of today. Since HDP is a cluster of different conditions including milder to severe variety, associations with air pollutants to both mild and severe categories of HDP examined separately will shed light on pathophysiology of HDP spectrum. Such understanding will help to develop preventive measures to reduce environmental contributor to HDP and HDP related unwanted pregnancy outcomes.

The associations between pollution and mild and severe categories of HDP are understudied in literature. Most of the existing studies are based on taking HDP as an umbrella diagnosis

outcome, and results of these studies are ambiguous regarding the associations between air pollution and HDP. This is the first large study to examine the relationship between ambient air pollution with gestational hypertension (GH) and preeclampsia- eclampsia (PE-E) separately with personal exposure data of $PM_{2.5}$ total mass and its constituents. This is a retrospective cohort study with an extensive literature review on patient population of Southern California Kaiser Permanente (KPSC) that includes 15 hospitals and 234 medical offices across Southern California with personal exposure data from residential addresses using fine-resolution geoscience-derived models' data for $PM_{2.5}$ total mass and its constituents for the period of 2008 to 2017. Data on demographic characteristics, including race, smoking status, insurance type, income category, residential history, medical records, birth records for maternal age, first pregnancy status, and individual lifestyle were collected from KPSC electronic health record (EHR) system. Information on gestational hypertension (GH), preeclampsia (PE) and eclampsia (E) were collected from the EHR using International Classification of Disease 9th and 10th revision (ICD-9 and ICD-10) codes for diagnosis.

The descriptive statistics of selected demographic and pregnancy characteristics and air pollution levels were conducted that showed a total of 431,800 cases, with a prevalence of 4.7% (n= 20310) for GH, 5.3% (n=22,678) for preeclampsia and 0.1% (n=313) for eclampsia. There were no significant age differences between GH group and PE-E group. Prevalence of both GH and PE-E were highest among Hispanic mothers (44.1% and 54.1%, respectively), followed by non-Hispanic White mothers (34.6% and 21.1%, respectively). There were no significant differences in the prevalence of either of the conditions based on mothers' education level, household income, smoking status, and season of conception. Prevalence of both the conditions were higher in primiparous women than respective controls [GH: 53.7% (non-GH: 40.8%) and PE-E: 56.6%

(non-PE-E: 40.3%)]. Additionally, while the prevalence of both the conditions were less among underweight [GH: 0.9% (non-GH: 2.6%), PE-E:1.5%, (non-PE-E: 2.5%)] and normal body mass index (BMI) [GH: 22.9% (non-GH: 44.9%), PE:27.5%, (non-PE-E: 43.7%)] mothers than non-cases, there was no differences in the prevalence of either GH or PE-E among overweight mothers and higher prevalence of both the conditions among obese mothers [GH: 21.3% (non-GH: 14.5%), PE-E:21%, (non-PE-E: 14.8%)].

Associations between air pollution exposures during entire pregnancy and the risk of GH and PE-E was estimated by multivariate Cox regression analysis. Positive associations were observed between PE-E and black carbon, $PM_{2.5}$ total mass and organic matter [Hazard Ratio (HR):1.12, CI:1.07-1.16, HR: 1.06, CI:1.03-1.08 and HR:1.06, CI:1.03-1.08 respectively]. Sensitivity analysis was conducted after further adjusting the model for pre-pregnancy Body Mass Index (BMI), primiparity and season, results consistent with that of the base model were observed for both GH and PE-E groups. To investigate whether differences in the associations among different race/ethnicity, pre-pregnancy BMI categories, mothers of different smoking habits and mothers from different economic condition exist, stratified analysis was conducted by race/ethnicity, maternal pre-pregnancy BMI, mother's smoking status and house-hold income categories. It was observed that slightly low risks of PE-E are associated with exposures to sulphate among White mothers with significant heterogenicity (Cochrane p value: 0.04), but for the GH group, maximum negative associations were observed among Asian American mothers in exposure to most of the pollutants with significant heterogenicity (Cochrane p value: <0.01). There were no significant differences in the risks of PE-E among mothers of different BMI categories; However, the GH group shows most negative associations to exposure ammonium in underweight mothers and to exposure to $PM_{2.5}$ total mass, nitrate, organic matter and black

carbon in the groups of normal body weight category, all with significant heterogenicity (Cochrane p value <0.05). For smoking subgroup analysis, the current smoker category shows no significant associations of risks in exposure to any of the pollutants (Cochrane p value: <.05). For the GH group, negative associations are observed in exposure to black carbon most among current smoker mothers, followed by past and never smoker pregnant women. For the subgroup analysis of house-hold income, highest risk of PE-E is seen among mothers with household income than $43,667 in exposure to black carbon with significant heterogenicity (Cochrane p value: <.01); while in the GH group, upper economic condition mothers (household income > $71, 591) were seen to be most protective of risk of developing GH in exposure to black carbon (Cochrane p value: <.01).

This study shows that exposure to air pollution with $PM_{2.5}$ total mass and two of its constituents, black carbon and organic matter, increases risks to develop severe forms of HDP, while there is no statistically significant association with milder HDP.

CHAPTER 1: INTRODUCTION AND PURPOSE

1.1 Introduction

Particles suspended in the air in various forms of solid, liquid or gas that are blended in complex mixture constitute air pollution. These pollutants are comprised of particulate matter (PM) of various aerodynamic diameters, such as particular matter with an aerodynamic diameter <10 μm (PM_{10}) or, finer PM with an aerodynamic diameter <2.5μm ($PM_{2.5}$) and various gases such as ozone, nitrogen dioxides, volatile organic compounds, and carbon monoxides. All of these components, particularly $PM_{2.5}$ have been shown to have highest adverse impact on human body through deposits in the lung, activating inflammatory process releasing mediators resulting in imbalance in autonomic nervous system and neuroendocrine system (Thangavel et al., 2022). One study conducted in US Metropolitan places reported that an increase in mean life expectancy of 0.61 ± 0.20 year is associated with a decrease of $PM_{2.5}$ concentration by 10 μg m^{-3} (Pope et al., 2009). There are increased evidences of ill health-effects of ambient air pollution, with cardiovascular and respiratory mortality representing the majority of the health outcomes (Samet, Jonathan & Daniel Krewski, 2003; Stieb et al., 2002). One meta-analysis by Stieb et al. that extracted effect sizes of 109 time series studies from around the world revealed that particulate matters of all sizes and the gaseous pollutants increase the all causes mortality (Stieb et al., 2002). Another Toronto based study by Stieb et al. reported statistically strong positive association between increase of $PM_{2.5}$ during warm season and increase in disability days from Canada National Population Health Survey data collected during the period of 1994-1999 (Stieb

et al., 2002). One recent study in Southern California showed that daily respiratory admissions increase by 0.76% [95% confidence interval (CI): 0.42-1.1] with a 10 μg m^{-3} increase in $PM_{2.5}$ (Aguilera et al., 2021). Two randomized, double blind cross-over studies conducted in Toronto and Michigan with 50 and 30 subjects respectively exposing them to fine particles of 150 μg m^{-3} and ozone of 120 parts per billion, each for 2 hours on 3 occasions, showed a significant increase in diastolic blood pressure by 2.6 to 4 mm Hg in both locations in the concentrated ambient $PM_{2.5}$ exposed group (Brook et al., 2009). Other good number of studies exist establishing a stronger relationship linking ambient fine particulate matter and cardiovascular risks including elevated blood pressure (Fan et al., 2019; Lin et al., 2017), so these associations on cardiovascular health during pregnancy should deserve special considerations.

Since pregnancy is an altered hemodynamic state with different cardiovascular parameters, hypertensive disorders in pregnancy (HDP) are unique conditions that need to be investigated separately to examine the associations with environmental factors. HDP, which complicates 5% to 10% of pregnancies, is a major cause of maternal and fetal morbidity and mortality (August, 2022). Understanding specific environmental contributors to HDP would help to take preventive measures to reduce the gestational disease burden. There are only a few studies that have been conducted showing ambient air pollution linking to HDP, but most of these studies show conflicting results of both positive or null associations or even negative associations due to inadequate sample sizes, different methods of exposure assessments, or broad non-specific outcome consideration as HDP (Braunthal & Brateanu, 2019; Dadvand et al., 2013; Jia et al., 2020; Nobles et al., 2019a; Pereira et al., 2013; Y. Shen et al., 2022; Wu et al., 2009a; Yan et al., 2022).

To analyze the outcome assessment of HDP, it is important to go over the HDP classification, which is based on the severity of clinical features. HPD is classified into 4 categories by American College of Obstetricians and Gynecologists (ACOG): gestational hypertension (GHTN), preeclampsia (PE), chronic hypertension with superimposed preeclampsia and eclampsia (E); classification is shown in Table 1.

Table 1. ACOG classification of hypertensive disorders in pregnancy

Terminologies	**Definitions** (Espinoza et al., 2020)	**Prevalence, %**	**Placental vascular involvement with multisystem dysfunction?** (Braunthal & Brateanu, 2019)
GH	SPB≥140 mmHg or a DBP ≥90 mmHg, or both, on 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive woman (Espinoza et al., 2020)	5-10 (M. Shen et al., 2017)	No
Chronic hypertension	SPB≥140 mmHg or a DBP ≥90 mmHg, or both at least 4 hours apart before 20 weeks of gestation	3-5 (Seely & Ecker, 2014)	No; general cardio-vascular involvement not specific to placental vasculatures
Pre-eclampsia	GH and one of the following: Proteinuria (≥ 300 mg per 24 hours urine collection, or protein/creatinine ratio ≥0.3	2-5 (Hutcheon et al., 2011)	Yes

	mg/dL or dipstick reading ≥2+ or in the absence of proteinuria, new onset hypertension (SPB≥140 mmHg or a DBP ≥90 mmHg) and any of the following: -thrombocytopenia (platelet count < 100,000 x 10^9/L -serum creatinine concentration >1.1 mg/dL, or doubling of serum creatinine concentrations in absence of other disease -elevated concentrations of liver transaminases to twice the normal concentration -pulmonary edema -new onset headache unresponsive to medication and not accounted by alternative diagnosis or visual symptoms (Espinoza at. Al, 2020)		

Hemolysis, Elevated Liver Enzymes and Low Platelet count (HELLP) syndrome	LDH ≥ 600 IU/dL, AST and ALT > twice the upper limit of normal levels, and platelet count < 100,000 x 10^9/L (Espinoza et al., 2020)	0.5-0.9 (Khalid et al., 2022)	Yes
Superimposed preeclampsia	When women with chronic hypertension develops signs of preeclampsia (Banala et al., 2020)	0.2-1 (Banala et al., 2020)	Yes
Eclampsia	HDP with convulsive manifestations	<1 (Wellington & Mulla, 2012)	Yes

In simple words, HDP with isolated elevated blood pressure with no systemic involvement is GH and HDP with organ involvement or systemic manifestations constitute preeclampsia including HELLP syndrome or superimposed preeclampsia and eclampsia.

1.2 Objective of Present Study

The primary objective of this study is to investigate the relationship between HDP and maternal residential exposures to $PM_{2.5}$ total mass and its five constituents (i.e., sulfate, ammonium, nitrate, organic matter and black carbon) in a large population-based pregnancy cohort based on Southern California Kaiser Permanente (KPSC) electronic health record (EHR) data between 2008 and 2017, with specific aims to i) examine the associations between exposure to $PM_{2.5}$ total mass and its five constituents (sulfate, nitrate, ammonium, organic matter and black carbon) and milder category of HDP, i.e., GH, ii) examine the associations between exposure to $PM_{2.5}$ total mass and its five constituents (sulfate, nitrate, ammonium, organic matter and black carbon) with severe category of HDP, i.e., PE-E and iii) examine the relationships with different constituents of $PM_{2.5}$. The primary hypothesis of this study is that increased level of $PM_{2.5}$ and its constituents are associated with increased risk of developing HDP, the associations between HDP and air pollution will differ by milder category of HDP, i.e., GH and severe category of HDP, i.e., PE-E and the $PM_{2.5}$ constituents are differentially associated with the risk of HDP.

CHAPTER 2: LITERATURE REVIEW

1.1 Fine Particulate Matter

Fine particulate matter is a complex mixture of different constituents, such as elemental, organic and black carbon, sulfate, nitrate and ammonium, and previous studies have documented their different physicochemical properties and toxic effects on human health, mostly on cardiovascular and respiratory systems (Achilleos et al., 2017; Dai et al., 2014; Valdés et al., 2012). Traffic and combustion, vegetation, atmospheric photochemical reaction are sources for elemental (or black) and organic carbon, while fossil fuel combustion and biogenic activities generate nitrates and sulfates from secondary oxidation of nitrogen oxides and sulfur gases (Achilleos et al., 2017). All these $PM_{2.5}$ constituents have various chemical compositions that generate from myriad of sources including outdoor sources like forest fire emissions, waste burning from agriculture and mineral dust blown by wind, incomplete fuel combustion and also from secondary emissions such as combustion and non-combustion processes that include residential energy use, traffic vehicles, energy generation, solvent use, industrial processes and agricultural fertilizer application (McDuffie et al., 2021).

According to a 2014 study, global $PM_{2.5}$ chemical composition proportion from the GEOS-Chem global chemical transport model is illustrated in Figure 1 (Philip et al., 2014). As represented in the pie chart, the mean $PM_{2.5}$ components were documented to be mostly sulfate, nitrate, ammonium, total secondary inorganic aerosol, particulate organic mass, black carbon, mineral dust and sea salt (Philip et al., 2014). Majority of $PM_{2.5}$ total mass is composed of heavy metals, minerals including dust and sea salt, inorganic ions, biological materials and polycyclic aromatic

hydrocarbons, volatile organic compounds and aryl hydrocarbons (Thangavel et al., 2022). Concentration and relative composition of $PM_{2.5}$ may be different in different regions depending of certain parameters such as season, wind speed, relative humidity, temperature, impervious land cover, cultivating land and so on (Stowell et al., 2020).

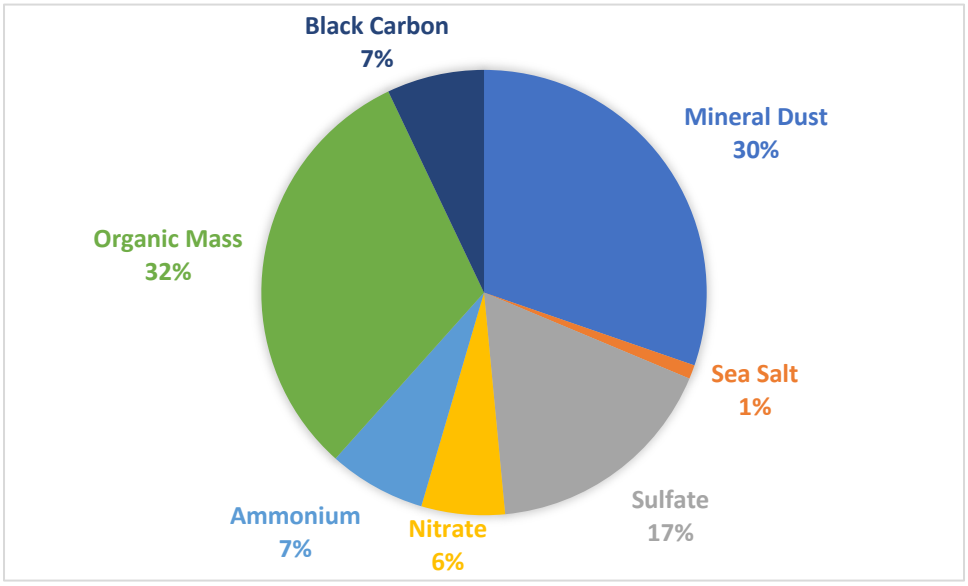

Figure 1: Global mean chemical composition of PM2.5 by Philip et al., 2014

The concentration of all $PM_{2.5}$ constituents have increased alarmingly in certain parts of the world mostly from industrial sources and carbonaceous combustions from vehicles. According to a 2020 study, in large cities of China the concentration ranges from 50 to 125 $\mu g/m^3$, much above than World Health Organization (WHO) labeled hazardous concentration of 10 $\mu g/m^3$ (Fu et al., 2020). Similarly, the population-weighed concentrations in Sub-Saharan Africa and Western Asia and Northern Africa were estimated to be in the range of 39.1$\mu g/m^3$ to 42.7 $\mu g/m^3$ by a WHO report from 2020 (Shaddick et al., 2020). Global Burden of Disease (GBD) database 2019, that analyzed associations of HDP with epidemiological data and socio-economic factors, has recognized HDP as one the first three causes of maternal morbidity and mortality, and relates its association with exposure to high $PM_{2.5}$, in addition to socio-economic factors (Wang et al., 2021).

$PM_{2.5}$ from different sources have been shown consistently to have negative impacts on human health, mostly on cardiovascular system (CVS) through different mechanisms as shown in Figure 1. Though chemical composition of fine particulate matter in different geographical locations are different depending on sources of emission, basic compositions are more or less same and most of them have been shown to affect blood pressure and heart rate through alteration of CVS physiology (Hamanaka & Mutlu, 2018; Mukherjee & Agrawal, 2017). The $PM_{2.5}$ and its constituents penetrate easily and enter mostly through lungs and to some extent, through the oropharyngeal and nasopharyngeal structures, and initiate changes of the CVS in chronic exposure to air pollution through following mechanisms: 1. stimulate the autonomic nervous system (ANS) with more sympathetic discharges that cause increased secretion of

catecholamines; 2. activation of lung macrophages and release of cytokines, such as interleukin - 6 (IL-6) and tumor necrosis factor-∝ (TNF-∝) through reactive oxygen species (ROS) with systemic inflammation; and 3. direct deposition on different tissues (e.g., gut, CVS, adipose tissue and liver), increasing systemic inflammation. All of these factors lead to vasoconstriction, endothelial dysfunction and cardiac electrical changes manifesting in clinical conditions like hypertension, atherosclerosis and cardiac arrythmias.

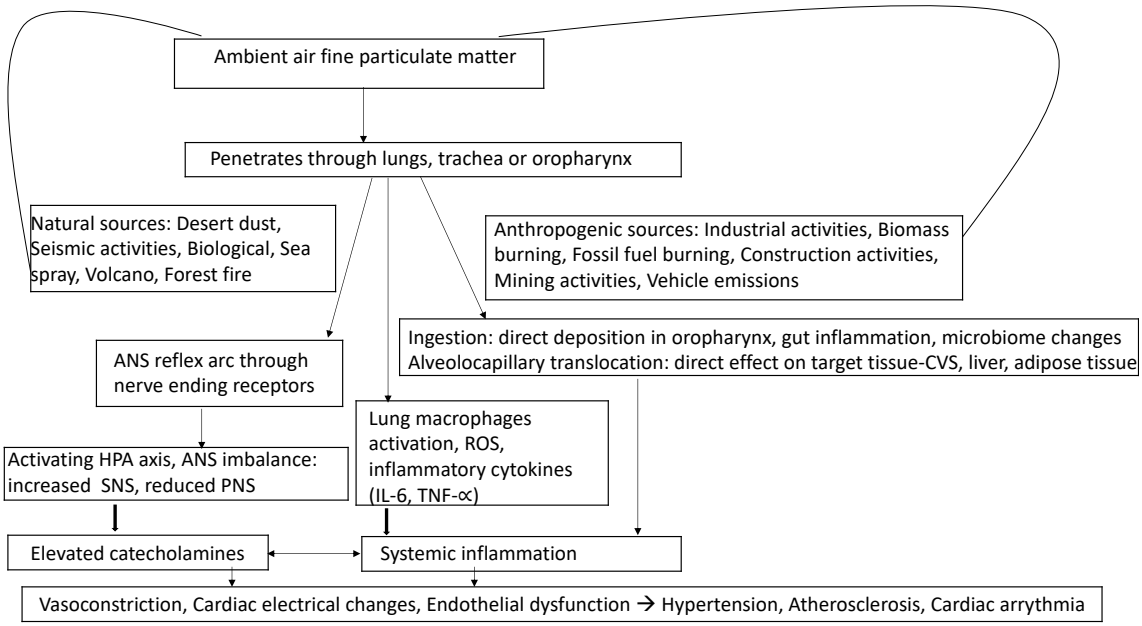

Figure 1. Fine particulate matter originating from different sources globally (Mukherjee & Agrawal, 2017) and its impact on cardiovascular system (Hamanaka & Mutlu, 2018).

ANS: Automatic Nervous System, CVS: Cardiovascular system, HPA: Hypothalamic Pituitary Axis, IL-6: Interleukin-6, PNS: Parasympathetic Nervous System, ROS: Reactive Oxygen Species, SNS: Sympathetic Nervous System, TNF-∝: Tissue Necrosis Factor-∝.

1.2 Critical cardiovascular dynamic during normal pregnancy and HDP

There are physiological changes of CVS parameters during normal pregnancy to adapt to the need of increased metabolic demand while carrying the fetus; these changes are summarized in

table 2. There is significant increase of blood volume by 30% to 50% that reach maximum during the second trimester, this hypervolemia causes an increase in the cardiac output (Baldisseri, Marie, 2015). There is a compensatory increase in heart rate by 15 to 20 beats per minute to maintain the high cardiac output (Baldisseri, Marie, 2015). With the progressive increase of cardiac output, maternal oxygen consumption also increases, and maternal oxygenation increases to a highest of 20% towards the term, which also contribute to physiological hyperventilation during pregnancy (Baldisseri, Marie, 2015). Thus, significant hyperventilation risks inhalation of more air pollutants or ambient toxic substances during pregnant condition. At the same time, there are vasodilation and decreased systemic vascular resistance that subsequently cause a decline in blood pressure in normal pregnancy and, this drop in blood pressure is more prominent during the second trimester (Baldisseri, Marie, 2015). In preeclampsia, which actually is a cardio-renal condition involving renin-angiotensin-aldosterone system, these parameters are altered with low cardiac output and high peripheral vascular resistance, and in severe preeclampsia this hypervolemic CVS physiology is even reversed with contraction of plasma volume (Gyselaers & Thilaganathan, 2019).

Table 2: CVS hemodynamic changes in normal pregnancy and HDP (based on Baldisseri, Marie, 2015 and Gyselaers & Thilaganathan, 2019)

Physiologic parameters	Normal pregnancy	HDP
Cardiac output	Elevated by 30%-50%	GH=no appreciable change PE-E= no increase or decrease
Blood volume	Elevated by 30%-50%	Variable; contracted in severe PE
Heart rate	Increased by 15 to 20 bpm	Variable, may increase more
Blood pressure	Decrease by 10 to 15 mmHg in second trimester	Elevated
Systemic vascular resistance	Decreases	Increases
Oxygen consumption	Increases by 20%	Variable

E: Eclampsia, GH: Gestational Hypertension, PE-E: Preeclampsia-Eclampsia, bpm: beats per minute

1.3 The association between air pollution and HDP

Although the ambient air pollutants are known to cause essential hypertension, the existing epidemiological findings regarding the effect of $PM_{2.5}$ on HDP are inconsistent. Pathophysiology of GH is thought to be distinct from that of preeclampsia in terms of placental vasculature changes and alterations in angiogenic factors (Melamed et al., 2014), so ambient pollutants may have differential effects on each of these entities of HDP. Most previous studies have mentioned the effects of ambient air pollutants on HDP as one entity, not separating out the effects on GH and PE-E. Since the implicated mechanisms in PE-E involve chronic uteroplacental ischemia from maternal angiogenic imbalance with a changed interaction between vasoactive cytokines, vasospasm is a significant finding in PE-E (Phipps et al., 2019; Ying et al., 2018), as opposed to GH. The effect of air pollution on pregnant mice has been documented in animal study by Weldy et al. 2014 on cardio-vascular system with increased blood pressure of pregnant mice getting exposed to exhausted diesel (Weldy et al., 2014). Another recent animal study on pregnant mice exposed to a mixture of urban pollutants showed that exposed mice placentae had hyperproliferation of syncytotrophoblasts, cytotrophoblasts, immune Natural Killer (NK-) cells and decidual type cells with depleted stromal cells and other types of immune cells like macrophages, granulocytes and endodermal cells (Tosevska et al., 2022). These findings are indicative of differential effect of air pollution on GH and PE-E. While exact pathophysiology of PE-E is unclear yet, the proposed pathway is illustrated in Figure 2.

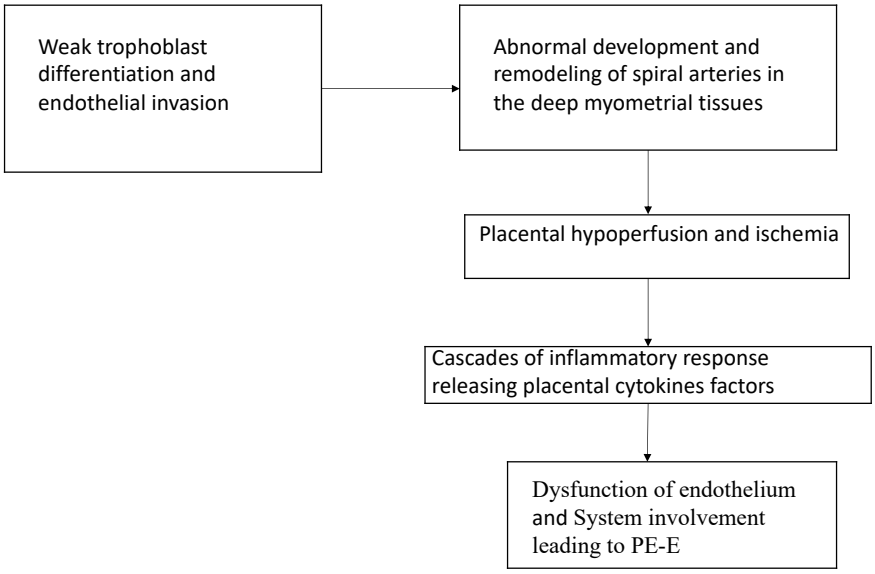

Figure 2. Proposed pathogenesis of pre-eclampsia (Bhojwani & Agrawal, 2022), showing cascades in placental vasculature involvement in initiating PE-E.

Previous studies have shown the both positive and negative associations between HDP and air pollutants (Dadvand et al., 2013; Lee et al., 2013; Nobles et al., 2019b; Pereira et al., 2013; Wu et al., 2009b; Zhu et al., 2017) but none of them have shown a clear association between air pollutants and different categories of HDP. Wu et al. in 2009 examined the association between preeclampsia and traffic-generated pollutants such as NOx and $PM_{2.5}$, and showed an increased risk of overall preeclampsia from exposure to NOx and $PM_{2.5}$, [odds ratio (OR) of 1.33, 95% CI, 1.18-1.49 and OR of 1.42 with CI 1.26-1.59, respectively)] in South Coast Air Basin of California population. Lee et al.2013 investigated the associations of exposure to $PM_{2.5}$ and GH and preeclampsia in Pennsylvania Allegheny county population and showed that exposure to $PM_{2.5}$ was associated increased risk of GH ($PM_{2.5}$ OR = 1.11, 95% CI = 1.00-1.23) with

insignificant results for preeclampsia risk; however, monitoring station data from the US Environment Protection Agency (EPA) based kriged air pollution was used in this study for PM_{10}, $PM_{2.5}$ and O_3, incorporated with air monitoring data by local county health department zip code level daily average concentrations calculated by space-time ordinary kriging; $PM_{2.5}$ species were not examined and eclampsia was not included in this study. Dadvand et al. 2013 study on Barcelona, Spain population showed that an interquartile range (IQR) increase in exposure to $PM_{2.5}$ by 7.3 $\mu g/m^3$ during the entire pregnancy was associated with preeclampsia risk with an OR of 1.32 (95% CI: 1.02, 1.71). However, this study was limited by only 103 cases of preeclampsia without specification about eclampsia, and with no information about GH. A study in Western Australian (Pereira et al. 2012) observed a 12% increased risk of preeclampsia with per IQR increase in levels of traffic-related air pollution in the entire pregnancy; this study also did not mention about GH and eclampsia. Previous studies thus were either incomplete and found insignificant, or even negative associations. Also, most of these studies were limited by use of US EPA based hourly monitoring data only for the criteria pollutants, not measuring $PM_{2.5}$ constituents, which may lack in individual level exposure assessment (Jia et al., 2020; Nobles et al., 2019a). Nobles et al. 2019 examined the relationships on Salt Lake City population showing an increased risk of GH from second trimester exposure to NOx (relative risk:1.18, CI 1.10-1.26) and lower risk of preeclampsia from first trimester exposure to NOx (relative risk:0.91, CI 0.84-0.99). However, eclampsia cases were excluded in the study population. Jia et al. 2020 studied the association in Hebei, China and reported that exposure to $PM_{2.5}$ was an independent risk factor for preeclampsia [OR:1.014 (95% CI: 1.00-1.028), 1.026 (95% CI: 1.012-1.049)] in first and second trimester, respectively, while no differences were observed for preeclampsia risk in exposure to average concentration of sulfur-di-oxide and carbon monoxide. This study model

was not adjusted for maternal smoking status and living habits and did not include data on GH outcome.

There is still a lack of investigations on the effects of ambient air pollution, particularly effect of the $PM_{2.5}$ and its constituents on different categories of HDP, as none of the existing literatures have explored the association with the severe and mild categories of HDP. One animal study conducted by Gao et al. in China on pregnant rats revealed that there were no significant differences in the increase of systolic blood pressure between the group exposed to $PM_{2.5}$ mixed air with the control (Gao et al., 2021). However, there was an altered inflammatory cell balance in the form of reduction in regulatory T-cell and helper T-cell ratios in exposed preeclampsia-like rats than control preeclampsia-like rat model (Gao et al., 2021). It implies that exposure to $PM_{2.5}$ during pregnancy act in a more complex manner triggering the inflammatory cells in the setting of preeclampsia than isolated effect on the blood pressure. Therefore, it is important to investigate the associations on GH and PE-E separately to provide evidence that will shed light on the underlying mechanisms and will assist in developing preventive measures for the child-bearing population and future generation.

There are two recent studies from China (Y. Shen et al., 2022; Yan et al., 2022) that attempted to examine the association between air pollution and GH and PE-E, separately; both in these studies, regional exposure based on delivery hospital zip codes were used for exposure assessment, instead of individual residential exposure. Yan et al. 2022 observed a 11% increased risk of GH per 10 $\mu g/m^3$ increase of $PM_{2.5}$ in the entire pregnancy and insignificant association with PE in China on a small sample subject of 3,754. Shen et al. 2022 in China with an average

sample size of 67,659 observed that an IQR increase in $PM_{2.5}$ exposure during the second trimester was associated with a 14% increase in HDP risk with 95% CI of 2% to 29% with larger effect estimate of black carbon and sulfate on GH than on the PE-E. However, neither of these studies were adjusted for maternal nutrition and smoking status.

In summary, the previous studies were lacking in many aspects including outcome measurement without specific HDP sub-categories, not including eclampsia cases in the study population, small sample sizes, not controlling the study for maternal smoking and lifestyle and finally none of the studies examining the associations of HDP with exposure to $PM_{2.5}$ species. This study was undertaken to address the knowledge gap of effect of pollution on milder and severe categories of HDP including GH, PE, and eclampsia. It was conducted to link those outcomes to exposure to PM2.5 and its five constituents that were obtained from monthly concentrations in ambient air from 2007 to 2017 measured by fine-resolution geoscience-derived models for personal level exposures to these pollutants and this study was controlled for sociodemographic characteristics including maternal smoking status and activity level.

CHAPTER 3: METHODOLOGY

To investigate the relationship between HDP risks and exposure to air pollution, this retrospective cohort study was conducted based on EHR data from KPSC that includes 15 hospitals and 234 medical offices across Southern California.

2.1 Study population

The participants were patient population of women with singleton pregnancy giving births from January 1, 2008, to December 31, 2017. KPSC EHR is the source of information on demographic characteristics, including maternal age, race/ethnicity, education, smoking status during pregnancy, insurance type, residential history, medical records, birth records, parity, and individual lifestyle. A total of included 386,425 pregnancies were included in the primary analysis after excluding participants with the following criteria (Figure 3): pregnancies who were not KPSC members or with gestational age < 20 or > 47 weeks, pregnancies with multiple fetus, participants without residential address. Pregnancies with presence of chronic hypertension (n = 14,179) were further excluded from GH group. Date of last menstrual period (LMP) coupled with early pregnancy ultrasonography were utilized to determine the gestational age. If there were a discrepancy between LMP and early pregnancy ultrasound report, the date found on the later was given preference based on recent ACOG guidelines (ACOG, 2017).

This study obtained the approval from the International Review Board of KPSC and the University of California, Irvine.

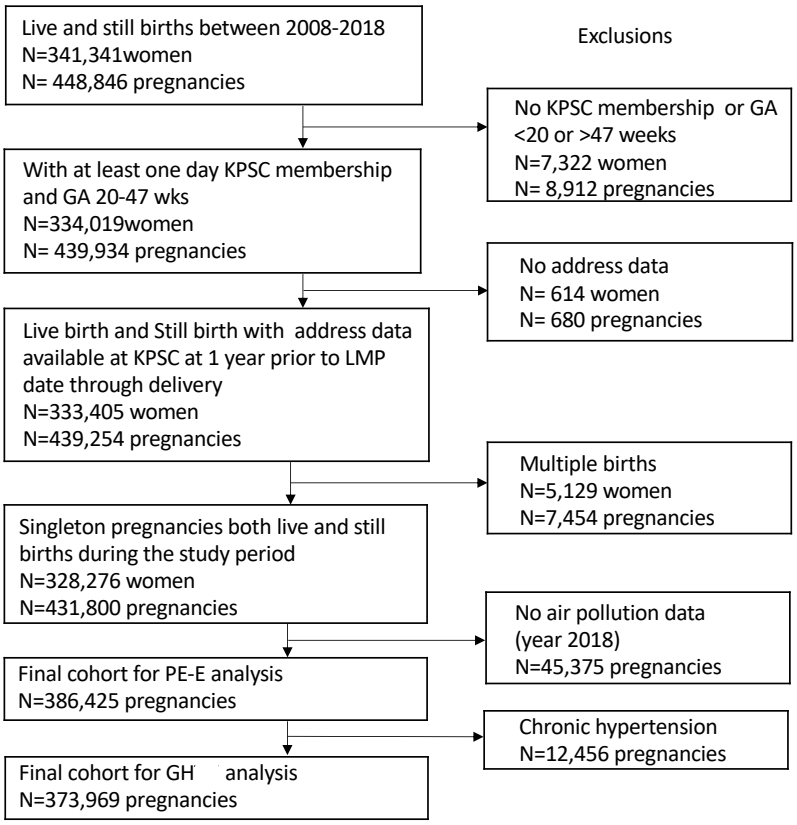

Figure 3. Schematic flowchart for the study design with exclusion criteria.

2.2 Outcome: GH, preeclampsia, superimposed preeclampsia, and eclampsia

Diagnosis of GH and PE-E were defined by ICD-9 and ICD-10 disease diagnostic codes. Pregnant women are screened for hypertension during each prenatal visit. GH, and PE-E were diagnosed after 20 weeks of gestation based on the criteria in Table 1. The participants were divided into two groups: 1) with GH, and 2) PE-E group with any one of the following: preeclampsia, preeclampsia superimposed upon chronic hypertension, or eclampsia. Cases with history of chronic hypertension were excluded from GH cohort as per the diagnostic criteria of GH.

2.3 Air pollution exposure

$PM_{2.5}$ total mass and constituents (i.e., sulfate, nitrate, ammonium, organic matter, and black carbon) monthly concentrations from 2007 to 2017 were obtained from fine-resolution geoscience-derived models developed by Dalhousie University, Canada (Meng et al. 2019b; van Donkelaar et al., 2019). Validated and publicly available $PM_{2.5}$ outputs at a 1-km resolution is provided by this model over North America that included chemical transport modeling (GEOS-Chem), satellite remote sensing of aerosol optical depth, and ground-based observations combining with a geographically weighed regression. This model for $PM_{2.5}$ species has high long-term cross-validation agreement with a R^2 value of 0.57-0.96 (van Donkelaar et al., 2019) and the $PM_{2.5}$ mass thus measured were close to ground $PM_{2.5}$ concentrations since 1999 (R^2: 0.6 -0.85) (Meng et al., 2019a). The consistent values agreement for $PM_{2.5}$ constituents ranging from 0.42 to 0.78.

Residential addresses during pregnancy were geocoded to utilize for spatiotemporal linking to each woman for air pollution estimates. KPSC EHR was used to abstract information on residential histories, including residential address, start and end dates of residency. The monthly air pollution metric was interpolated to generate daily exposures conception date to delivery date using the TIMESERIES Procedure of the SAS 9.4 software (SAS institute, Cary, NC). Entire pregnancy was defined for the period from the conception date to the date of diagnosis for cases or the date of delivery for non-cases and exposure during entire pregnancy was calculated using Cox multivariate analysis.

2.4 Covariates

Covariates and potential confounders were selected based on HDP clinical guidelines (ACOG 2022), and existing literature (Wilkerson et al., 2019, Brown et al., 2019) from KPSC EHRs,

including maternal age, race/ethnicity (African/American, non-Hispanic Asians, Hispanic, non-Hispanic White, and others including Pacific Islanders, Native American/Alaskan and, mothers with multiple race/ethnicities specified) and educational level (less than 8th grade, 9th grade to high school graduates, less than 4 years of college, more than 4 years to less than 5 years of college and more than 5 years of college); median household income at block group level in 2013 (CDC, 2020) (categorized it in four income groups: less than $43,667, $43,667 to $55,929, $55930 to $71,591 and above $71,591); pre-pregnancy body mass index [(BMI, kg/m^2) , underweight (<18.5), normal wight (18.5-24.9), overweight (25.0-29.9), obese class 1 (30.0-34.9), obese class 2 (35.0-39.9) and obese class 3 (>40.0)]; exposure to active and passive second hand smoke during pregnancy; season of conception (warm; May-October; cool; November-April), health insurance status (two groups: on Medical or Medicare and other kinds of health insurance including private) and years of infant birth. Zip code Tabulation Areas defined by the U.S. Census Bureau were used to represent zip codes (*Https://Www.Census.Gov*, 2010varia).

2.5 Statistical Analysis

Descriptive statistics were performed with distribution of selected population characteristics and exposure to $PM_{2.5}$ total mass and constituents comparing pregnant women with and without GH or PE-E. Correlation between air pollution metrics was estimated with Pearson's correlation. Cox proportional hazard models were performed to examine the associations between each air pollutant ($PM_{2.5}$ total mass and five $PM_{2.5}$ constituents) and each outcome during the entire pregnancy, and non-cases were censored at delivery. Per IQR increment of each individual air pollutant was used to calculate HRs and 95% CIs. The main model was adjusted for maternal age, race/ethnicity, education, household income, smoking, passive smoker status during

pregnancy and year of infant birth. Zip code was fitted as a random effect to account for potential spatial clustering for diseases. Further, sensitivity analyses were carried out to examine the influence of pre-pregnancy BMI, primiparity (first pregnancy) and season of conception, as there are epidemiological evidence of these factors altering the risks for HDP. For example, high BMI (>30) and primiparity are listed as recognized risk factors for HDP in ACOG practice guidelines ("Gestational Hypertension and Preeclampsia," 2020); previous epidemiological studies have shown that preeclampsia risk depending on season of conception, with purported mechanism of low vitamin D during cold weather or more infectious disease prevalence during summer in certain geographical locations (Wellington & Mulla, 2012; Yan et al., 2022). Additionally, subgroup analysis was conducted to examine stratified effects of race/ethnicity (African/American, non-Hispanic Asians, Hispanic and non-Hispanic White), pre-pregnancy BMI, primiparity and smoking. SAS version 9.4 was used to conduct all the analysis.

CHAPTER 4: RESULTS

3.1 Population characteristics

The descriptive statistics of selected demographic and pregnancy characteristics and air pollution levels are presented in Table 3. In total, 4.8% (17,989/373,969) and 5.0% (19,383/386,425) of eligible pregnancies were GH and PE-E cases, respectively. Among PE-E group, 19,336 cases of PE, 3,054 cases of preeclampsia superimposed upon chronic hypertension, and 283 cases of eclampsia were identified.

Hispanic mothers suffered most from both GH (44.1%) and PE-E (54.1%), followed by non-Hispanic White mothers for both the two categories: GH (34.6%) and PE-E (21.1%); while there is marginal higher frequency of GH among Asians (9.8%), comparing to that of African Americans (8.1), the frequency of PE-E among these two groups are same (11.0%-11.1%). In addition, levels of education do not make a difference on the frequency of GH or PE-E. Mothers with college education of four and five years has most frequencies of both GH (32.1%) and PE-E (30.7%), on the other hand, frequencies of these conditions among mothers with more than five years of college education is 32.1% and that of preeclampsia-eclampsia is 31.8%, whereas mothers with college education of less than four years of college education has frequencies of GH and pre-eclampsia-eclampsia are 24.2% and 25.9% respectively. Interestingly, categories of less than eight grade have least incidence of both GH (0.6%) and PE-E (0.7%) and mothers with high school education of 9^{th} grade to high school have almost same frequencies of GH 30.2% and of PE-E 31.6%, as higher educational level mothers.

Median household income does not seem to effect GH and PE-E either comparing to the non-GH or non-PE-E groups. All the categories of median household income, less than $43,667 income

group, $43,667-$55,929 and $55,930-$71,591 have prevalence of GH and PE-E similar to that of respective non-cases groups (range is 24.9% to 25.2%) in the range of 24.6% to 24.3%, with lower frequency of PE-E in other income group (i.e., in the income group above $71,591) with 20.7%. Regarding the insurance type, pregnant women on Medical or Medicaid have slightly higher frequencies of both GH (8.8%) comparing to the non-GH group (9.7%) and pre-PE (10.5%) comparing to the non-PE-E group (9.6%), whereas there are no significant differences in the outcomes of interest in the non-MediCal/Medicaid insurance group.

There are no significance differences of frequencies of GH, or PE-E in warm and cool seasons. There are slightly more frequencies of GH (50.4%), than in the non-GH group (49.3%) during warm season of conception, but slightly less frequencies of GH (49.4%) than that of non-GH group (50.6%) during cold season of conception. Opposite prevalence is observed in the PE-E group with slightly less frequencies (48.7%) than non-PE-E group (49.3%) during warm season and marginally higher frequencies (51.3%) than non-PE-E group (50.6%) during cold season. Non-smoker pregnant women has slightly less frequencies of both GH (79.5%, non-GH:83.8%) and PE-E (82.5%, non-PE-E:83.5%), previously smoking pregnant women has slightly more frequencies of GH (13.6%, non-GH:11.2%) with same frequencies of PE-E (11.9%, non-PE-E: 11.3%). Interestingly, for currently smoking pregnant women, while there is somewhat more prevalence of GH (6.9%, non-GH: 5%), there is no differences of prevalence of PE-E (5.6%) comparing to the non-PE-E group (5.1%). There are no differences in the frequencies of any of GH or PE-E based on passive smoking status.

Primiparous women have more frequencies of both GH (53.7%, non-GH = 40.8) and PE-E (56.6%, non-PE-E: 40.3%) and the frequencies are less among non-primiparous pregnant women (GH: 46.3%, non-GH: 59.2% and PE-E :43.4%, non-PE-E:59.7%). Considering pre-pregnancy BMI, categories of underweight and normal body weight pregnant women have less frequencies of both GH (0.9%, 22.9%, non-GH: 2.6%, 44.9% respectively) and PE-E (1.5%, 27.6%, non-PE-E: 2.5%, 43.7%, respectively). There are no differences in frequencies of both GH and PE-E in overweight category (ranging from 28.1% to 28.5% for all cohorts of cases and non-cases). There is increased frequencies of both GH and PE-E in the categories of obese class 1 (GH :21.3, non-GH:14.5, PE-E=21.0%, non-PE-E:14.8%), obese class 2 (GH :14.2, non-GH:6.4, PE-E:12.9%, non-PE-E:6.8%), and obese class 3 (GH:12.3, non-GH:3.4, PE-E:9.8%, non-PE-E:4%).

Table 3. Description of the study population and air pollution levels by maternal characteristics, 2008-2017.

Characteristics	Total births, N = 373,969	Gestational hypertension, N =17,978	Non-GH N =355,991	Total births, N = 386,425	Pre-eclampsia +Eclampsia, N=19,383	Non-PE-E N=367,042
Maternal age, years, mean (SD)	30.3(5.9)	30.7(5.9)	30.0(5.8)	30.3(6.1)	30.5(6.3)	30.1(5.8)
Maternal race/ethnicity (N, %)						
African American	27878 (7.5)	1485(8.3)	26393(7.4)	29669(7.7)	2198(11.3)	27471(7.5)
Non-Hispanic Asian	46772(12.5)	1746(9.7)	45026(12.7)	48277(12.6)	2097(10.8)	46180(12.6)
Hispanic	191719(51.3)	7872(43.8)	183847(51.7)	197146(51.0)	10454(53.9)	186692(50.9)
Non-Hispanic white	98076(26.2)	6288(35.0)	91788(25.8)	101380(26.2)	4099(21.2)	97281(26.5)
Multiple/other	9488(2.5)	583(3.2)	8905(2.5)	9914(2.6)	532(2.8)	9382(2.6)
Maternal education (N, %)						
≤ 8th Grade	4014(1.1)	113(0.6)	3901(1.1)	4133(1.1)	156(0.8)	3957(1.1)
9 Grade to High School	115269(31.4)	5392(30.6)	109877(31.5)	118653(31.3)	6071(32.0)	112582(31.3)
< College	84455(23.0)	4276(24.2)	80179(23.0)	87522(23.1)	4924(26.0)	82598(23.0)
College (< 4 years)	115011(31.4)	5646(32.0)	109365(31.3)	119058(31.4)	5748(30.3)	113310(31.5)
College (≥ 4 years)	47832(13.1)	22221(12.6)	45611(13.1)	49440(13.1)	2051(10.8)	47389(13.1)
Block group median household income in 2013 (N, %)						
<$43,667	93257(25.0)	4395(24.5)	88880(25.1)	96459(25.1)	5722(29.6)	90737(24.8)
$43,667-$55,929	93266(25.0)	4458(24.9)	88808(25.0)	96505(25.1)	4962(25.7)	91543(25.0)
$55,930-$71,591	92965(24.9)	4510(25.2)	88630(25.0)	96108(25.0)	4688(24.2)	91420(25.0)
> $71,591	93192(25.0)	4562(25.5)	88630(25.0)	96035(25.0)	3960(20.5)	92075(25.2)
Smoking (N, %)						
Never Smoker	311714(83.4)	14237(79.2)	297477(83.6)	321650(83.3)	15918(82.1)	305731(83.3)
Ever Smoker	42443(11.4)	2438(13.6)	40005(11.2)	44216(11.4)	2332(12.0)	44216(11.4)
Smoking during pregnancy	19759(5.3)	1302(7.2)	18457(5.2)	20504(5.3)	1130(5.8)	19374(5.3)

Passive smoker (N, %)						
Yes	8360(2.3)	444(2.5)	7916(2.2)	8573(2.2)	498(2.6)	8075(2.2)
No	363307(97.8)	17516(97.5)	345791(97.8)	375545(97.8)	18829(97.4)	356716(97.8)
Pregnancy order (N, %)						
Primiparous	172850(41.4)	10907(53.7)	161943(40.8)	165001(40.3)	12881(56.6)	177882(41.2)
Not first pregnancy	244771(58.6)	9403(46.3)	235368(59.2)	253918(58.8)	9859(43.4)	244059(59.7)
Pre-pregnancy body mass index (N, %)						
Underweight (<18.5)	9564(2.6)	156(0.9)	9408(2.7)	9619(2.5)	282(1.5)	9337(2.6)
Normal weight (18.5-24.9)	163969(44,3)	4173(23.4)	159796(45.3)	165768(43.3)	5363(27.9)	160405(44.1)
Overweight (25.0-29.9)	104343(28.2)	5037(28.3)	99306(28.2)	107243(28.0)	5362(27.9)	107243(28.0)
Obese class1 (30.0-34.9)	54220(14.6)	3777(21.2)	50443(14.3)	57348(15.0)	4033(21.0)	53315(14.7)
Obese class2 (35.0-39.9)	24577(6.6)	2510(14.1)	22067(6.3)	26762(7.0)	2326(12.1)	24436(6.7)
Obese class3 (>40.0)	13865(3.7)	2169(12.2)	11696(3.3)	16235(4.2)	1843(9.6)	14392(4.0)
Insurance type (N, %)						
MediCal (or Medicaid)	34038(9.3)	1495(8.4)	32543(9.3)	35133(9.2)	1918(10.0)	33215(9.2)
Other	333568(90.7)	16285(91.6)	317283(90.7)	344744(90.8)	17207(90.0)	327537(90.8)
Season of conception (N, %)						
Warm season	184747(49.4)	9088 (50.6)	175659(49.3)	190788(49.4)	9407(48.5)	181381(49.4)
Cool season	189222(50.6)	8890 (49.5)	180332(50.7)	195637(50.6)	9976(51.5)	185661(50.6)

SD, standard deviation.

3.2 The relationship between air pollution metrics Summary statistics and Pearson correlation coefficients between air pollution metrics during the entire pregnancy are presented in table 4. $PM_{2.5}$ total mass concentrations were highly correlated with most $PM_{2.5}$ chemical constituents, including $PM_{2.5}$ organic matter (r = 0.91), nitrate (r=0.86), black carbon (0.79), and ammonium (r=0.75), and moderately correlated with $PM_{2.5}$ sulfate (r = 0.49). Relatively weaker correlations were noticed between sulphate with other $PM_{2.5}$ constituents with values equal or below 0.46. Moderate to strong correlations were observed between other $PM_{2.5}$ constituents (nitrate, ammonium, organic matter and black carbon) with values equal to or above 0.53.

3.3 The association between air pollution and GH, PE-E

To examine the associations of risks of GH and PE-E and exposures to air pollution during the entire pregnancy, multivariate Cox regression models were conducted for each air pollutant separately. Results are illustrated in Figure 4. No significant associations are observed between the risk of GH and $PM_{2.5}$ and its five constituents. On the other hand, the risks of PE-E are positively associated with $PM_{2.5}$ total mass and two $PM_{2.5}$ constituents: black carbon has the highest risk for PE-E (HR=1.11, 95% CI=1.07-1.15), followed by $PM_{2.5}$ total mass (HR=1.07, 95% CI=1.04-1.10) and organic matter (HR=1.05, 95% CI=1.03-1.08). All the results in this analysis are statistically significant with p value of <0.0001.

Table 4. Summary statistics and Pearson correlation coefficients between air pollution exposure metrics during pregnancy.

	Mean (SD)	IQR	$PM_{2.5}$ total mass	$PM_{2.5}$ Sulfate	$PM_{2.5}$ Nitrate	$PM_{2.5}$ Ammonium	$PM_{2.5}$ Organic matter	$PM_{2.5}$ Black carbon
$PM_{2.5}$ total mass	12.86 (2.60)	3.85	1.00					
$PM_{2.5}$ sulfate	1.27 (0.26)	0.35	0.49	1.00				
$PM_{2.5}$ nitrate	2.41 (0.64)	0.94	0.86	0.36	1.00			
$PM_{2.5}$ ammonium	0.95 (0.32)	0.40	0.75	0.46	0.80	1.00		
$PM_{2.5}$ organic matter	5.39 (1.30)	1.78	0.91	0.35	0.66	0.55	1.00	
$PM_{2.5}$ black carbon	1.48 (0.61)	1.05	0.79	0.25	0.54	0.53	0.72	1.00

SD, standard deviation; IQR, interquartile range; The units for $PM_{2.5}$ and $PM_{2.5}$ constituents are $\mu g/m^3$.

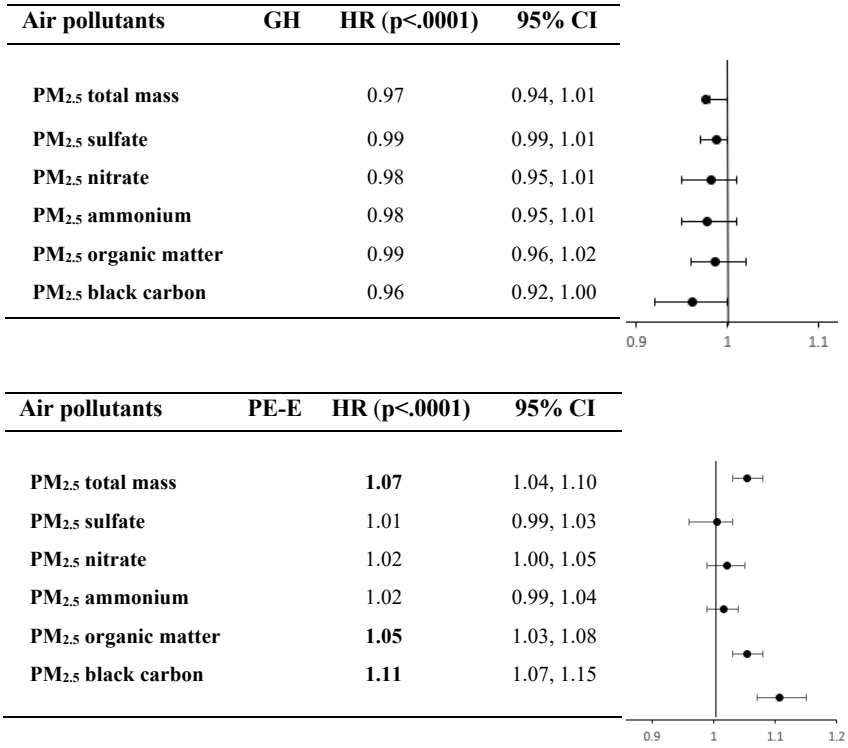

Figure 4. Adjusted hazards ratios (HRs) and 95% confidence intervals (CI) of GH and PE-E associated with air pollution during the entire pregnancy.

GH, Gestational hypertension. PE-E, Preeclampsia-Eclampsia.

Hazards ratio (HR)s and 95% CIs were calculated for per interquartile range (IQR) increment for each air pollutant. Model adjusted for year of birth, maternal age, race/ethnicity, education, block group household income, smoking and passive smoking status. Zip code was fitted as a random effect. Significant results were bolded.

3.4 Results of Sensitivity Analysis

Table 5 shows the results of the base model with further adjusting for pre-pregnancy BMI, primiparity and season of conception. Comparing to the results from base model, the GH group showed negative associations with exposure to $PM_{2.5}$ and its constituents; while positive associations similar to base model between air pollution and PE-E were observed after further adjusting for pre-pregnancy BMI, first pregnancy and season of conception. After further adjusting the model for pre-pregnancy BMI, results consistent with that of the base model were observed for the PE-E group, whereas, for the GH group statistically significant negative associations are observed with exposure to $PM_{2.5}$ total mass, nitrate, and ammonium [HRs: 0.95 (CI: 0.93, 0.98), 0.96 (CI: 0.93,0.99) and 0.96 (CI:0.93, 0.99) respectively]. Then, further adjusting the model for primiparity, again consistent results were observed for the PE-E group, and, for the GH group statistically significant negative association is observed with exposure to $PM_{2.5}$ total mass [HRs: 0.96 (CI: 0.94, 0.99)]. On further adjusting the model for season, similar pattern is observed for PE-E group and statistically significant negative association is observed in exposure to $PM_{2.5}$ total mass, organic matter, and black carbon in the GH group [HRs: 0.96 (CI: 0.93, 0.99), 0.96 (CI: 0.93,0.99) and 0.91 (CI:0.87, 0.95) respectively]. In short, statistically significant negative associations to certain $PM_{2.5}$ constituents were observed in the GH group on sensitivity analysis for pre-pregnancy BMI, primiparity and season.

Table 5. Adjusted hazard ratios (HRs) and 95% confidence intervals (CI) of GH and PE-E associated with air pollution during the entire pregnancy in sensitivity analysis.

Pollutants	GH HRs	95% CI		PE-E HRs	95% CI	
Base model, further adjusted for pre-pregnancy BMI						
$PM_{2.5}$ total mass	**0.95**	**0.93**	**0.98**	**1.04**	**1.02**	**1.07**
$PM_{2.5}$ sulfate	0.98	0.96	1.00	0.99	0.97	1.01
$PM_{2.5}$ nitrate	**0.96**	**0.93**	**0.99**	1.01	0.98	1.04
$PM_{2.5}$ ammonium	**0.96**	**0.93**	**0.99**	1.01	0.98	1.03
$PM_{2.5}$ organic matter	0.97	0.94	1.00	**1.05**	**1.02**	**1.08**
$PM_{2.5}$ black carbon	0.95	0.91	1.00	**1.11**	**1.07**	**1.15**
Base model, further adjusted for first pregnancy						
$PM_{2.5}$ total mass	**0.96**	**0.94**	**0.99**	**1.04**	**1.01**	**1.06**
$PM_{2.5}$ sulfate	0.98	0.96	1.00	1.00	0.98	1.03
$PM_{2.5}$ nitrate	0.96	0.93	1.01	1.03	1.00	1.06
$PM_{2.5}$ ammonium	0.93	0.90	0.96	1.01	0.99	1.03
$PM_{2.5}$ organic matter	0.97	0.94	1.00	**1.05**	**1.02**	**1.08**
$PM_{2.5}$ black carbon	0.97	0.93	1.01	**1.10**	**1.05**	**1.14**
Base model, further adjusted for season						
$PM_{2.5}$ total mass	**0.96**	**0.93**	**0.99**	**1.06**	**1.04**	**1.09**
$PM_{2.5}$ sulfate	1.00	0.97	1.03	0.99	0.96	1.01
$PM_{2.5}$ nitrate	0.96	0.93	0.99	1.03	1.00	1.06
$PM_{2.5}$ ammonium	0.96	0.93	0.98	1.02	1.00	1.04
$PM_{2.5}$ organic matter	**0.96**	**0.93**	**0.99**	**1.07**	**1.04**	**1.90**
$PM_{2.5}$ black carbon	**0.91**	**0.87**	**0.95**	**1.13**	**1.09**	**1.17**

GH: gestational hypertension; PE-E: preeclampsia-eclampsia. N=373,969 for GH cohort; N=386,425 for PE-E cohort. Hazards ratio (HR)s and 95% CIs were calculated for per interquartile range (IQR) increment for each air pollutant. Base model adjusted for maternal age, race/ethnicity, maternal education, household income, maternal smoking status, insurance type, and year of birth; zip code was fitted as a random effect.

3.5 Results of Subgroup Analysis

Subgroup analysis was conducted stratified by maternal race/ethnicity, pre-pregnancy BMI, maternal smoking and household income to examine the differences among those population subgroups. Table 6 shows the results from subgroup analyses.

In the GH cohort, there is negative associations in most of the subgroups with exposures to all the pollutants with significant heterogenicity (p value <0.01) except for exposure to sulfate. For the race/ethnicity and BMI subgroup, risk of GH is seen to be least among Asians mothers with normal pre-pregnancy BMI in exposure to the pollutants with significant heterogenicity (p value<.001). For the smoking subgroups, paradoxically, current smokers during pregnancy are observed to be at least risk for developing GH followed by past smokers and never smokers in exposure to black carbons with significant heterogenicity (p value<.001). For house-hold income category, pregnant mothers with house-hold income more than $71,591 are observed to be at to be at least risk of developing GH followed by the income group of $43,667 to $55,930 and income group of $55,930 to $71,591 in exposure to black carbon with significant heterogenicity (p value<.001). The negative association trend for GH in the income categories was similar in case of the other $PM_{2.5}$ constituents.

In the PE-E cohort, positive associations are observed in exposure to the pollutants, but the differences in associations are not statistically significant in most subgroups. In the race/ethnicity subgroup, negative association of PE-E with exposures to sulfate is observed among non-Hispanic White with significant heterogenicity (p value .04). On the hand, for house-hold income category, increased risk for developing PE-E is observed among pregnant mothers with house-

hold income less than $43,667, followed by income category of 43,667 to $55,930 and that of $55,930 to $71,591 respectively, with significant heterogenicity (p value .03).

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Table 6. Adjusted hazard ratios (HRs) and 95% confidence intervals (CI) of GH and PE-E associated with air pollution during the entire pregnancy among population subgroups.

Air pollution	Characteristics	GH HRs	95%	CIs	p value for Cochrane's Q test	PE-E HRs	95%	CIs	P value for Cochrane's Q test
Maternal race/ethnicity									
$PM_{2.5}$ total mass	African American	0.89	0.80	1.00	<0.01	1.06	0.99	1.15	0.98
	Asian	0.80	0.72	0.88		1.05	0.95	1.15	
	Hispanic	0.92	0.88	0.97		1.07	0.92	1.12	
	Non-Hispanic white	0.97	0.92	1.02		1.07	0.95	1.21	
$PM_{2.5}$ sulfate	African American	0.99	0.93	1.07	0.23	0.99	0.98	1.06	0.04
	Asian	1.03	0.97	1.10		1.04	0.98	1.10	
	Hispanic	0.97	0.94	1.00		1.02	1.00	1.04	
	Non-Hispanic white	1.00	0.97	1.03		0.95	0.91	0.99	
$PM_{2.5}$ nitrate	African American	0.87	0.78	0.96	<0.01	1.08	1.05	1.17	0.34
	Asian	0.82	0.74	0.90		0.98	0.91	1.06	
	Hispanic	0.95	0.91	0.99		1.02	0.99	1.05	
	Non-Hispanic white	0.99	0.95	1.04		1.03	0.98	1.08	
$PM_{2.5}$ ammonium	African American	0.86	0.78	0.94	<0.01	1.05	0.99	1.14	0.45
	Asian	0.83	0.77	0.91		0.97	0.95	1.04	
	Hispanic	0.95	0.91	0.99		1.03	0.98	1.06	
	Non-Hispanic white	0.97	0.93	1.02		1.01	0.97	1.06	
$PM_{2.5}$ organic matter	African American	0.95	0.86	1.05	<0.01	1.02	1.01	1.10	0.67
	Asian	0.85	0.78	0.93		1.06	1.01	1.15	
	Hispanic	0.95	0.91	0.99		1.06	0.98	1.10	
	Non-Hispanic white	0.98	0.94	1.02		1.08	1.01	1.13	

$PM_{2.5}$ black carbon	African American	0.87	0.76	0.99	<0.01	1.11	1.09	1.23	0.72
	Asian	0.71	0.63	0.80		1.06	1.01	1.15	
	Hispanic	0.89	0.84	0.97		1.08	1.01	1.10	
	Non-Hispanic white	0.90	0.84	0.97		1.08	1.01	1.13	
Pre-pregnancy BMI									
$PM_{2.5}$ total mass	Underweight	0.84	0.67	1.01	<0.01	1.10	0.90	1.35	0.47
	Normal	0.86	0.80	0.91		1.09	1.03	1.14	
	Overweight	0.88	0.83	0.93		1.06	1.00	1.11	
	Obese	0.91	0.87	0.96		1.04	1.00	1.08	
$PM_{2.5}$ sulfate	Underweight	0.85	0.70	1.04	0.02	0.97	0.83	1.13	
	Normal	0.99	0.95	1.03		0.99	0.95	1.03	
	Overweight	0.94	0.90	0.97		1.01	0.96	1.04	
	Obese	1.00	0.97	1.03		0.99	0.97	1.03	
$PM_{2.5}$ nitrate	Underweight	0.82	0.64	1.06	<0.01	0.98	0.82	1.17	0.33
	Normal	0.89	0.84	0.95		1.05	1.00	1.10	
	Overweight	0.92	0.87	0.97		1.01	0.97	1.06	
	Obese	0.93	0.89	0.97		0.99	0.96	1.03	
$PM_{2.5}$ ammonium	Underweight	0.73	0.57	0.94	<0.01	1.02	0.86	1.21	0.49
	Normal	0.92	0.87	0.97		1.04	1.00	1.09	
	Overweight	0.88	0.83	0.92		0.99	0.92	1.04	
	Obese	0.94	0.90	0.97		1.01	0.97	1.04	
$PM_{2.5}$ organic matter	Underweight	0.96	0.76	1.21	<0.01	1.04	0.94	1.39	0.68
	Normal	0.90	0.85	0.95		1.07	1.02	1.12	
	Overweight	0.94	0.89	0.98		1.04	1.00	1.10	
	Obese	0.94	0.90	0.98		1.04	1.00	1.08	
$PM_{2.5}$ black carbon	Underweight	0.78	0.55	1.09	<0.01	1.27	0.98	1.66	0.20
	Normal	0.75	0.70	0.81		1.16	1.09	1.23	

	Overweight	0.85	0.79	0.91		1.14	1.07	1.21	
	Obese	0.90	0.85	0.95		1.08	1.03	1.14	
Smoking status during pregnancy									
$PM_{2.5}$ total mass	Never smoker	0.96	0.93	1.00	0.12	1.07	1.00	1.10	0.53
	Past smoker	0.90	0.84	0.97		1.11	1.03	1.10	
	Current smoker	0.95	0.86	1.04		1.05	0.95	1.16	
$PM_{2.5}$ sulfate	Never smoker	0.99	0.97	1.02	0.40	1.01	0.99	1.03	0.17
	Past smoker	0.96	0.91	1.01		0.97	0.91	1.02	
	Current smoker	1.02	0.94	1.09		1.06	0.98	1.15	
$PM_{2.5}$ nitrate	Never smoker	0.98	0.95	1.02	0.18	1.02	1.00	1.05	0.75
	Past smoker	0.93	0.86	0.99		1.05	0.98	1.12	
	Current smoker	0.95	0.87	1.03		1.03	0.94	1.12	
$PM_{2.5}$ ammonium	Never smoker	0.98	0.95	1.01	0.02	1.02	0.99	1.15	0.74
	Past smoker	0.90	0.84	0.96		1.02	0.96	1.08	
	Current smoker	0.97	0.89	1.05		1.03	0.94	1.14	
$PM_{2.5}$ organic matter	Never smoker	0.97	0.94	1.01	<0.01	1.05	1.02	1.08	0.11
	Past smoker	0.95	0.89	1.01		1.13	1.06	1.22	
	Current smoker	0.97	0.89	1.05		1.03	0.94	1.14	
$PM_{2.5}$ black carbon	Never smoker	0.94	0.90	0.98	<0.01	1.11	1.07	1.15	0.26
	Past smoker	0.86	0.78	0.94		1.18	1.08	1.29	
	Current smoker	0.85	0.76	0.96		1.05	0.92	1.20	
Household income									
$PM_{2.5}$ total mass	< $43,667	0.98	0.91	1.04	<0.01	1.10	1.04	1.16	0.23
	$43,667-$55,930	0.90	0.84	0.95		1.04	0.99	1.10	
	$55,930-$71,591	0.90	0.85	0.96		1.11	1.05	1.17	
	>$71,591	0.99	0.96	1.04		1.05	0.99	1.11	
$PM_{2.5}$ sulfate	< $43,667	0.97	0.93	1.01	0.27	0.99	0.95	1.02	0.09

	$43,667-$55,930	1.01	0.97	1.06		1.05	1.01	1.08	
	$55,930-$71,591	0.97	0.93	1.01		0.99	0.95	1.03	
	>$71,591	0.99	0.96	1.04		0.99	0.96	1.04	
$PM_{2.5}$ nitrate	< $43,667	1.01	0.96	1.07	<0.01	1.04	1.00	1.09	0.08
	$43,667-$55,930	0.90	0.85	0.96		0.99	0.95	1.04	
	$55,930-$71,591	0.92	0.87	0.98		1.08	1.02	1.13	
	>$71,591	0.93	0.88	0.99		1.01	0.95	1.06	
$PM_{2.5}$ ammonium	< $43,667	0.99	0.95	1.05	<0.01	1.08	1.03	1.14	0.09
	$43,667-$55,930	0.91	0.86	0.96		1.00	0.96	1.05	
	$55,930-$71,591	0.90	0.86	0.96		1.08	1.03	1.13	
	>$71,591	0.94	0.90	0.99		0.99	0.94	1.04	
$PM_{2.5}$ organic matter	< $43,667	0.98	0.93	1.04	<0.01	1.08	1.03	1.14	0.09
	$43,667-$55,930	0.92	0.87	0.97		1.01	0.97	1.06	
	$55,930-$71,591	0.95	0.89	1.01		1.10	1.05	1.16	
	>$71,591	0.94	0.89	0.99		1.06	1.00	1.12	
$PM_{2.5}$ black carbon	< $43,667	0.95	0.88	1.02	<0.01	1.20	1.12	1.28	
	$43,667-$55,930	0.83	0.77	0.90		1.12	1.05	1.19	
	$55,930-$71,591	0.86	0.80	0.93		1.13	1.06	1.21	
	>$71,591	0.84	0.78	0.91		1.04	0.97	1.13	

GH, Gestational hypertension. PE-E, Preeclampsia-Eclampsia; BMI, body mass index.

Hazards ratio (HR)s and 95% CIs were calculated for per interquartile range (IQR) increment for each air pollutant. Base model adjusted for maternal age, race/ethnicity, maternal education, household income, maternal smoking status, insurance type, and year of birth; zip code was fitted as a random effect.

CHAPTER 5: DISCCUSSION

This is a large retrospective cohort study of 386,425 pregnant participants who have been residing in Southern California from 2008 to 2017. This study is the first study to examine the associations between $PM_{2.5}$ constituents and GH and PE-E separately in a large and diverse population. Here, the results show that exposures to $PM_{2.5}$ total mass, organic matter and black carbon are associated with increased risk of PE-E, but not for GH. Also, it was observed that mothers who lived in low- to middle-income neighborhoods and mothers with normal pre-pregnancy BMI, overweight and obese groups are associated with increased risk for PE-E on exposure to black carbon. Additionally, Asian mothers with normal pre-pregnancy BMI are observed to be at least risk of developing GH followed by Hispanic normal pre-pregnancy BMI mothers in exposure to all the pollutants except for sulfate. Furthermore, highest negative associations of risk of GH in exposure to the pollutants were observed in mothers of upper income neighborhood.

The finding of positive associations between HDP and black carbon has been supported by a recent study (Y. Shen et al., 2022). Another recent study in China showed positive association between $PM_{2.5}$ and GH with null effect on PE-E (Yan et al., 2022). On the contrary, our study found opposite results with positive associations between PE-E and $PM_{2.5}$ total mass, organic matter, and black carbon and null or negative associations for GH. Yan et al., 2022 measured the

outcome with physician-filled questionnaires instead of using diagnostic codes that might introduce some recall bias regarding the diagnosis, in addition to measurements limited to national monitoring station data for air pollution exposure assessment that lacked in individual level exposure. This study used ICD-9 and ICD-10 code for diagnosis of GH and PE-E collected from the EHR and pollution exposure was assessed utilizing fine-resolution geoscience-derived models based on individual residential address.

This study observes negative or null associations of $PM_{2.5}$ exposure with GH. Some of the $PM_{2.5}$ constituents may have common ingredients as smoking pollutants with tobacco smoke containing a combination of organic and inorganic particulate matter that is primarily composed of $PM_{2.5}$ and other gaseous and volatile compounds (Sheu et al., 2022). There is clear evidence of deleterious maternal and fetal health effects of tobacco smoking during pregnancy and conception; however, smoking has been paradoxically shown to be protective in all categories of HDP (Wei et al., 2015). Several mechanisms have been implicated to explain the decreased risk of HDP among smoker pregnant women (Lewandowska & Więckowska, 2020).
HDP can be considered mild when there is only GH that does not involve the organs and severe in presence of preeclamptic features, which is a muti-system disease. The mechanisms that are put forward in PE are compromised trophoblast invasion, release of placental vasoactive substances and placental hypoxia (Possomato-Vieira & Khalil, 2016). An imbalance between vasoactive substances including vasoconstrictive factors like Thromboxane A2, endothelin and vasodilator factors, such as prostacyclin and nitric oxide, have been demonstrated as one of the proposed mechanisms of preeclampsia (Possomato-Vieira & Khalil, 2016), while other studies stated that smoking might induce liver enzymes cytochrome P-450 which could metabolize those

vasoactive substances rapidly, thus clearing out those vasoconstrictive factors from the system (Zang et al., 1999). Likewise, the $PM_{2.5}$ constituents in ambient pollution may induce more break down of vasoconstrictive vasogenic factors by hepatic enzymes leading to vasodilatation and thus, not contributing to the risk for GH, which is the milder category of HDP. In fact, increased expression of cytochrome P-450 and induction of stress response enzymes, including glutathione transferase, heme oxygenase, superoxide mutase in epithelial cells and macrophages by $PM_{2.5}$ constituents have been documented in previous studies (Ghio et al., 2012). However, in cases of more severe forms of HDP spectrum including preeclampsia, HELLP syndrome and eclampsia, there is increased placental vasoconstrictive factors production as a result of exposure to the ambient pollution that overwhelm the cytochrome P450 enzymes induction system and thus, resulting in positive associations of pollution exposure with PE-E. Moreover, previous studies documented increased placental biomarker 3-nitrotyrosine and hypomethylated leptin promoters in placental tissue on exposure to black carbon and $PM_{2.5}$ (Saenen et al., 2016, 2017). These findings explain why risks for PE-E entities of HDP that are thought to have trophoblast invasion and placental vascular etiologies are increased by exposure to ambient pollutants, while the milder form of HDP (i.e., GH) may not be affected by these pollutants, or even may have been deceptively protected by some of those pollutants through non-placental mechanisms. These mechanistic pathways are explained in Figure. 5. Nevertheless, these pollutants have deleterious effect on pregnant health, and it is observed in this study that exposures to $PM_{2.5}$ total mass, black carbon and organic matter are positively associated particularly with the severe categories in the HDP spectrum.

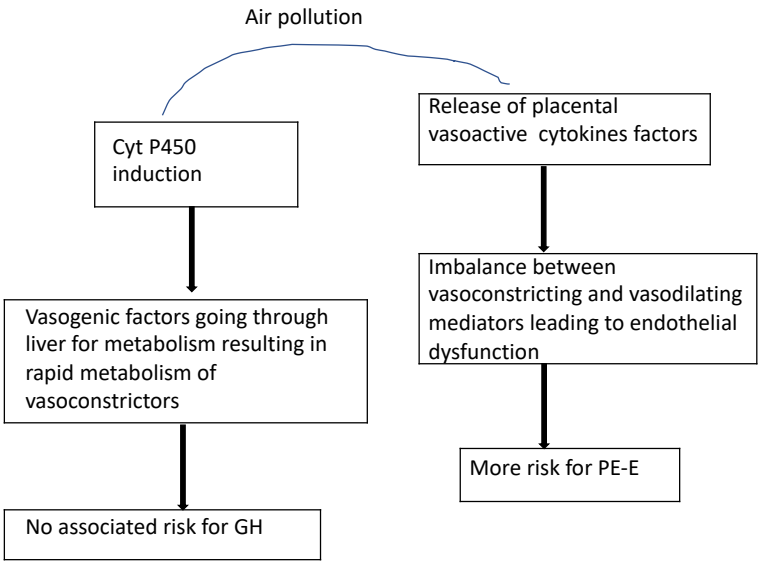

Figure 5. Differential pathway of pollution for GH and PE-E (Bhojwani & Agrawal, 2022)

Current study proposed mechanistic pathway for risks of gestational hypertension versus pre-eclampsia-eclampsia on exposure to ambient air pollution. GH: Gestational Hypertension; PE-E: Preeclampsia-Eclampsia.

This study's findings of positive association of severe variety of HDP with exposure to $PM_{2.5}$ total mass and black carbon have been supported by one Swedish study that observed increased risk of PE with an increment of [OR of 1.35 (95% CI of 1.11-1.63)] each 5 $\mu g/m^3$ locally emitted $PM_{2.5}$ and the risk of severe PE, as measured by the number of PE cases being complicated with small for gestational age (SGA) baby, has been shown to have stronger association with exposure to linear increases of black carbon by 1$\mu g/m^3$ [adjusted OR of 3.48 (95% CI 1.67-7.27)] (Mandakh et al., 2020). Another study conducted in Oakland, California with a sample size of 1059 mothers with hypothetical intervention by limiting black carbon level to the 25th percentile found that there was significant reduction in the risk of preeclampsia on reduced black carbon exposure (risk differences: -1.0, 95% CI: -2.2, 0.02) (Goin et al., 2021) and this finding support our result of positive association of PE-E with black carbon exposure.

Health and Policy Implications

Such research on environmental exposure and reproductive and developmental health issues is important in order to protect the reproductive health and to develop public policies. As both health and economic burdens increase dramatically with severity of HDP, more research is needed to understand the causes of those associations. Although everyone is affected by air pollution, the intensity may disproportionately be higher among women living in poverty and, subsequently increasing the risks of severe HDP among women of certain socio-economic background. Adding to the overwhelming body of evidence ranging from epidemiological studies to animal data revealing pollution as a leading cause of hypertension and CVS mortality, chronic inhalation exposure has been shown to accelerate those CVS changes in presence of underlying health condition and altered physiology, as mentioned by EPA ("Linking-Air-Pollution-and-Heart-Disease", 2022). Some of the predisposing factors for preeclampsia such as maternal obesity, inflammatory responses, hypercoagulable state, endothelial dysfunction are also found to be risk factors for CVS diseases. Therefore, true economic impacts of air pollution on hypertension and subsequent CVS diseases are likely far beyond the estimates, as it also includes maternal and child health with CVS diseases that occur under altered physiology of pregnancy. Besides, since women with preeclampsia require prolonged hospitalization and most often unplanned cesarean section for management, preeclampsia management involves significant increase in health care costs. In 2003, it was estimated to be $11208 per woman on average in the United States (Fox et al., 2017). Apparently, American Heart Association (AHA) has recognized preeclampsia as one of the independent risk factors of future CVS diseases and stroke, thus intensifying long term social and financial impact of the condition on the health care

system (Turbeville & Sasser, 2020). Since preeclampsia is a multi-system disease, it also affects other vital organs, psychological health, thus overall quality of life, knowing about the modifiable risk factors will help to inform health priorities and public policy. The toll of preeclampsia on fetal health is also heavy ranging from premature birth, intrauterine growth restriction and SGA babies. The most effective cure of the condition is delivery of placenta and fetus (Lu & Hu, 2019). According to one accepted theory called Developmental Origin of Health and Disease (DOHaD), offspring of preeclamptic mothers are at risk of developing chronic diseases in later life (Barker, David, 2006). Understanding the differential association of air pollution on mild and severe forms of HDP will help to educate the high-risk women to reduce the disease burden.

According to 2019 annals of global health (Boyd, 2019), the main source of air pollution globally is combustion of fossil fuels and biomass that are also significant source of short-lived climate pollutants like black carbon (South Africa et al., 2019). It was estimated in 2015 that air pollution global economic burden of disease across 176 countries was $3.8 trillion. Therefore, a call to action by five national Academies of Science and Medicine of South Africa, Brazil, Germany and United States was issued to government leaders, business and citizens to bring down air pollution in all countries (South Africa et al., 2019). Having clear evidence of association between air pollution and maternal and fetal health would help the policy makers to initiate multinational actions to mitigate those environmental effect on reproductive health and future generation.

Study Limitation and Strength

There are certain limitations in this study. As is inherent to retrospective study design, data was collected from the hospital EHR recorded by different examiners, that might introduce some intra-examiner variability. For the same reason, there was some missing variables for some of the demographic information that was not recorded in the EHR. Furthermore, since air pollution is such a universal exposure, it might overlap with some of the covariate data, like passive smoking.

Moreover, exposure assessment was done outside using residents' home addresses, so the study is limited by not having indoor source exposure assessment, as it did not include any indoor source exposure information. On the other hand, the dates of GH, preeclampsia and eclampsia diagnosis were collected from the EHR when the diagnosis code was entered and exposure based on the date of diagnosis was calculated, this date may not actually coincide with the start of the disease process, as these conditions may be asymptomatic initially until patients present into the clinic for routine screening and detected in a later date. Besides, demographic information such as smoking history including passive smoker status, household income, type of insurance was taken from the EHR system, that may not be as complete and accurate as survey information filled directly by the participants. Also, information on family history of PE-E was not included in this study.

Despite study limitations, this study represents strong evidence for several reasons. The major advantage of this study is that it is a multi-center study involving a large health-care system at Southern California that allowed large pool of participants, data included for an extended period of nine years. Large sample size of this study with repeated measures of the participants and robust statistical analysis conferred high power to the study. Since most of the previous studies

are on combined outcome of GH and preeclampsia taking them in the umbrella diagnosis of HDP, or pregnancy induced hypertension (PIH), this study addressed the gap in the literature to link the effect of pollution and different HDP spectrum. Here, data for different categories of HDP are collected from different ICD diagnostic codes, which is very specific. Secondly, a robust statistical model was used for analysis with adjusting the model for different possible socio-demographic factors and ACOG listed risk factors to avoid the confounding effect of the variables. The fact that there are very scant numbers of studies that exist until now establishing a clear effect of ambient pollutants on GH and PE-E, the current study should contribute to open a new avenue of further research to identify specific risk factors of different categories of HDP and to understand corresponding pathophysiology. This study targeted to elucidate the effect of $PM_{2.5}$ total mass and its five species on both milder and severe forms of HDP and to derive at a pathophysiologic understanding of the associations. Here a robust Cox multilevel analysis model was used, and the model was adjusted for socio-demographic confounders using large KPSC database.

Further studies utilizing personal air pollution data with active personal sampling of the pollutants will be helpful. Studies with use of blood biomarkers for exposure to the pollutants would show more accurate associations by minimizing confounding effects. For the diagnosis of preeclampsia, the severity of preeclampsia can be assessed with fetal complications like babies with SGA or maternal complications like abruption of placenta. Looking at the association of pollutants with severity of preeclampsia using indicators like SGA baby or cases with placental abruption would give additional insights of the effects of pollutants on HDP severity mechanistic pathway. As described by some literatures, there are two phases of preeclampsia-early onset

preeclampsia (preeclampsia diagnosed between 20 to 34 weeks of pregnancy) and late onset preeclampsia (preeclampsia after 34 weeks of pregnancy) (Raymond & Peterson, 2011), examining the associations between pollution with each of the following: GH, early onset preeclampsia, late onset preeclampsia, superimposed preeclampsia and eclampsia probably would be reveal more about the pathophysiology of HDP spectrum with different severity. Prospective observational study design with personal exposure data will allow to use better controls for better comparison with non-cases to get more compelling results. Complex statistical model with mixture analysis should give more composite effects of the pollutants. Finally, animal studies with GH and preeclampsia models and examining molecular changes on pollutant exposure for causation pathway are desirable for better understanding.

CHAPTER 6: CONCLUSION

Despite presence of sufficient evidence from all around the globe that air pollution is linked to CVS disorders in general population, there are only handful of evidence examining the relationships with HDP. As results of most of the existing literatures on the association between pollution and HDP being inconsistent, this study was conducted to find an answer to the question-are the associations of pollution with milder and severe forms of HDP are different? Given that existing body of evidence supporting probable mechanism of PE-E being involved placental endothelial factors as opposed to GH, the effect of pollution on PE-E is not same as that of GH. This study reveals positive association of pollution with PE-E and null association of pollution with GH supporting this hypothesis of differential associations. Even after controlling the study for socio-demographic characteristics like race, smoking, household income and insurance type and ACOG listed risk factors like pre-pregnancy BMI and primiparity, increased risk of PE-E from exposure to $PM_{2.5}$, organic matter and black carbon are observed and slightly decreased or null risk for GH is observed from exposure to the same pollutants. This study also finds that the risk of PE-E is increased in exposure to the pollutants among pregnant women with lower household income, showing the more harmful effect of the toxic pollutants on underserved population, thus highlighting the issue of environmental justice.

This research has implications in developing environmental health policy to prevent maternal and fetal morbidity and mortality. As CDC has provided Tracking Network to be used as surveillance methods by creating indicators for reproductive and birth outcome data that can be linked to environmental exposure or hazard data ("Reproductive and Birth Outcomes", 2020), this research finding will help to inform public health policy action. Also ACOG position paper has mentioned the importance of more research on pollution and toxic exposure on reproductive

and developmental health outcome for effective clinical intervention (BorderS, Ann, 2013). As according to WHO, preeclampsia related morbidity and mortality reduction is important to improve maternal and perinatal health globally ("WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia", 2011) , this study finding will assist in developing environmental guidance policy to prevent severe HDP worldwide.

References

Achilleos, Souzana, Marianthi-Anna Kioumourtzoglou, Chih-Da Wu, Joel D. Schwartz, Petros Koutrakis, and Stefania I. Papatheodorou. "Acute Effects of Fine Particulate Matter Constituents on Mortality: A Systematic Review and Meta-Regression Analysis." *Environment International* 109 (December 2017): 89–100. https://doi.org/10.1016/j.envint.2017.09.010.

Aguilera, Rosana, Thomas Corringham, Alexander Gershunov, and Tarik Benmarhnia. "Wildfire Smoke Impacts Respiratory Health More than Fine Particles from Other Sources: Observational Evidence from Southern California." *Nature Communications* 12, no. 1 (December 2021): 1493. https://doi.org/10.1038/s41467-021-21708-0.

August, Phyllis. "Https://Www.Uptodate.Com/Contents/Preeclampsia-Clinical-Features-and-Diagnosis," August 2022.

Baldisseri, Marie. *Https://Clinicalgate.Com/Cardiovascular-and-Endocrinologic-Changes-Associated-with-Pregnancy/*. Critical Care Medicine, 2015.

Banala, Chaitra, Sindy Moreno, Yury Cruz, Rupsa C. Boelig, Gabriele Saccone, Vincenzo Berghella, Corina N. Schoen, and Amanda Roman. "Impact of the ACOG Guideline Regarding Low-Dose Aspirin for Prevention of Superimposed Preeclampsia in Women with Chronic Hypertension." *American Journal of Obstetrics and Gynecology* 223, no. 3 (September 2020): 419.e1-419.e16. https://doi.org/10.1016/j.ajog.2020.03.004.

Barker, David.

"Https://Journals.Lww.Com/Clinicalobgyn/Fulltext/2006/06000/Adult_consequences_of_fetal_g

rowth_restriction.9.Aspx?Casa_token=t62RSAcyx8wAAAAA:NsasnR_vnBbJnlaTDsQcLJoqvbmzsV37mTPnroR-Cw0fG2dVyHjA1FRpKuI2fuiQdWf1XowU_A_XguxoZruyG7o," June 2006.

Bhojwani, Kashish, and Anil Agrawal. "Study of Histopathological Changes in the Placenta in Preeclampsia." *Cureus*, October 16, 2022. https://doi.org/10.7759/cureus.30347.

BorderS, Ann. "Https://Www.Acog.Org/Clinical/Clinical-Guidance/Committee-Opinion/Articles/2021/07/Reducing-Prenatal-Exposure-to-Toxic-Environmental-Agents," October 2013.

Boyd, D. R. (2019). The Human Right to Breathe Clean Air. *Annals of Global Health*, *85*(1), 146. https://doi.org/10.5334/aogh.2646

Brauer, Michael, Cornel Lencar, Lillian Tamburic, Mieke Koehoorn, Paul Demers, and Catherine Karr. "A Cohort Study of Traffic-Related Air Pollution Impacts on Birth Outcomes." *Environmental Health Perspectives* 116, no. 5 (May 2008): 680–86. https://doi.org/10.1289/ehp.10952.

Braunthal, Stephanie, and Andrei Brateanu. "Hypertension in Pregnancy: Pathophysiology and Treatment." *SAGE Open Medicine* 7 (January 2019): 205031211984370. https://doi.org/10.1177/2050312119843700.

Brook, Robert D., Bruce Urch, J. Timothy Dvonch, Robert L. Bard, Mary Speck, Gerald Keeler, Masako Morishita, et al. "Insights Into the Mechanisms and Mediators of the Effects of Air Pollution Exposure on Blood Pressure and Vascular Function in Healthy Humans." *Hypertension* 54, no. 3 (September 2009): 659–67. https://doi.org/10.1161/HYPERTENSIONAHA.109.130237.

Dadvand, Payam, Francesc Figueras, Xavier Basagaña, Rob Beelen, David Martinez, Marta Cirach, Anna Schembari, Gerard Hoek, Bert Brunekreef, and Mark J Nieuwenhuijsen. "Ambient Air

Pollution and Preeclampsia: A Spatiotemporal Analysis." *Environmental Health Perspectives* 121, no. 11–12 (November 2013): 1365–71. https://doi.org/10.1289/ehp.1206430.

Dai, Lingzhen, Antonella Zanobetti, Petros Koutrakis, and Joel D. Schwartz. "Associations of Fine Particulate Matter Species with Mortality in the United States: A Multicity Time-Series Analysis." *Environmental Health Perspectives* 122, no. 8 (August 2014): 837–42. https://doi.org/10.1289/ehp.1307568.

Donkelaar, Aaron van, Randall V. Martin, Michael Brauer, Ralph Kahn, Robert Levy, Carolyn Verduzco, and Paul J. Villeneuve. "Global Estimates of Ambient Fine Particulate Matter Concentrations from Satellite-Based Aerosol Optical Depth: Development and Application." *Environmental Health Perspectives* 118, no. 6 (June 2010): 847–55. https://doi.org/10.1289/ehp.0901623.

Fan, Fangfang, Shixuan Wang, Yi Zhang, Dandan Xu, Jia Jia, Jianping Li, Tiantian Li, Yan Zhang, and Yong Huo. "Acute Effects of High-Level PM $_{2.5}$ Exposure on Central Blood Pressure." *Hypertension* 74, no. 6 (December 2019): 1349–56. https://doi.org/10.1161/HYPERTENSIONAHA.119.13408.

Fox, Aimée, Sheena McHugh, John Browne, Louise C. Kenny, Anthony Fitzgerald, Ali S. Khashan, Eugene Dempsey, Ciara Fahy, Ciaran O'Neill, and Patricia M. Kearney. "Estimating the Cost of Preeclampsia in the Healthcare System: Cross-Sectional Study Using Data From SCOPE Study (Screening for Pregnancy End Points)." *Hypertension* 70, no. 6 (December 2017): 1243–49. https://doi.org/10.1161/HYPERTENSIONAHA.117.09499.

Fu, Haiyue, Yiting Zhang, Chuan Liao, Liang Mao, Zhaoya Wang, and Nana Hong. "Investigating PM2.5 Responses to Other Air Pollutants and Meteorological Factors across Multiple Temporal

Scales." *Scientific Reports* 10, no. 1 (December 2020): 15639. https://doi.org/10.1038/s41598-020-72722-z.

Gao, Jie, Mei Luo, Shuo Zhao, Hailing Wang, Xuan Li, Pili Xu, Wei Ma, and Chongdong Liu. "Effect of PM2.5 Exposure On Gestational Hypertension and Fetal Size in Preeclampsia-Like Rats." Preprint. In Review, September 20, 2021. https://doi.org/10.21203/rs.3.rs-872858/v1.

"Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222." *Obstetrics & Gynecology* 135, no. 6 (June 2020): e237–60. https://doi.org/10.1097/AOG.0000000000003891.

Ghio, Andrew J., Martha Sue Carraway, and Michael C. Madden. "Composition of Air Pollution Particles and Oxidative Stress in Cells, Tissues, and Living Systems." *Journal of Toxicology and Environmental Health, Part B* 15, no. 1 (January 2012): 1–21. https://doi.org/10.1080/10937404.2012.632359.

Goin, Dana E., Sylvia Sudat, Corinne Riddell, Rachel Morello-Frosch, Joshua S. Apte, M. Maria Glymour, Deborah Karasek, and Joan A. Casey. "Hyperlocalized Measures of Air Pollution and Preeclampsia in Oakland, California." *Environmental Science & Technology* 55, no. 21 (November 2, 2021): 14710–19. https://doi.org/10.1021/acs.est.1c02151.

Gyselaers, Wilfried, and Basky Thilaganathan. "Preeclampsia: A Gestational Cardiorenal Syndrome." *The Journal of Physiology* 597, no. 18 (September 2019): 4695–4714. https://doi.org/10.1113/JP274893.

Hamanaka, Robert B., and Gökhan M. Mutlu. "Particulate Matter Air Pollution: Effects on the Cardiovascular System." *Frontiers in Endocrinology* 9 (November 16, 2018): 680. https://doi.org/10.3389/fendo.2018.00680.

"Https://Cfpub.Epa.Gov/Ncer_abstracts/Index.Cfm/Fuseaction/Display.AbstractDetail/Abstract_id/7519," n.d.

"Https://Www.Acog.Org/Clinical/Clinical-Guidance/Practice-Bulletin/Articles/2020/06/Gestational-Hypertension-and-Preeclampsia," June 2020.

"Https://Www.Cdc.Gov/Nceh/Tracking/Topics/ReproductiveandBirthOutcomes.Htm," October 21, 2020.

"Https://Www.Census.Gov," 2010varia. https://www.census.gov/programs-surveys/geography/guidance/geo-areas/zctas.html.

"Https://Www.Census.Gov/Programs-Surveys/Geography/Technical-Documentation/Records-Layout/2010-Zcta-Record-Layout.Html," 2010. https://www.census.gov/programs-surveys/geography/technical-documentation/records-layout/2010-zcta-record-layout.html.

"Https://Www.Columbiacardiology.Org/Patient-Care/Womens-Heart-Center/about-Heart-Disease-Women/Pregnancy-and-Heart-Disease/Preeclampsia-and-Gestational-Hypertension," n.d.

"Https://Www.Epa.Gov/Sciencematters/Linking-Air-Pollution-and-Heart-Disease." Linking Air Pollution and Heart Disease, March 2022.

"Https://Www.Researchgate.Net/Profile/Arideep-Mukherjee/Publication/315733607_A_Global_Perspective_of_Fine_Particulate_Matter_Pollution_and_Its_Health_Effects/Links/5c5858f3458515a4c757e09d/A-Global-Perspective-of-Fine-Particulate-Matter-Pollution-and-Its-Health-Effects.Pdf," n.d.

"Https://Www.Who.Int/Publications/i/Item/9789241548335." WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia, November 2011.

Hutcheon, Jennifer A., Sarka Lisonkova, and K.S. Joseph. "Epidemiology of Pre-Eclampsia and the Other Hypertensive Disorders of Pregnancy." *Best Practice & Research Clinical Obstetrics & Gynaecology* 25, no. 4 (August 2011): 391–403. https://doi.org/10.1016/j.bpobgyn.2011.01.006.

Jia, Lu, Qing Liu, Huiqing Hou, Guangli Guo, Ting Zhang, Songli Fan, and Li Wang. "Association of Ambient Air Pollution with Risk of Preeclampsia during Pregnancy: A Retrospective Cohort Study." *BMC Public Health* 20, no. 1 (December 2020): 1663. https://doi.org/10.1186/s12889-020-09719-w.

Khalid, Farhan, Neetu Mahendraker, and Tiffany Tonismae. "HELLP Syndrome." In *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2022. http://www.ncbi.nlm.nih.gov/books/NBK560615/.

Lee, Pei-Chen, James M. Roberts, Janet M. Catov, Evelyn O. Talbott, and Beate Ritz. "First Trimester Exposure to Ambient Air Pollution, Pregnancy Complications and Adverse Birth Outcomes in Allegheny County, PA." *Maternal and Child Health Journal* 17, no. 3 (April 2013): 545–55. https://doi.org/10.1007/s10995-012-1028-5.

Lewandowska, Małgorzata, and Barbara Więckowska. "The Influence of Various Smoking Categories on The Risk of Gestational Hypertension and Pre-Eclampsia." *Journal of Clinical Medicine* 9, no. 6 (June 4, 2020): 1743. https://doi.org/10.3390/jcm9061743.

Lin, Hualiang, Yanfei Guo, Yang Zheng, Qian Di, Tao Liu, Jianpeng Xiao, Xing Li, et al. "Long-Term Effects of Ambient PM $_{2.5}$ on Hypertension and Blood Pressure and Attributable Risk Among Older Chinese Adults." *Hypertension* 69, no. 5 (May 2017): 806–12. https://doi.org/10.1161/HYPERTENSIONAHA.116.08839.

Lu, Hui Qing, and Rong Hu. "Lasting Effects of Intrauterine Exposure to Preeclampsia on Offspring and the Underlying Mechanism." *American Journal of Perinatology Reports* 09, no. 03 (July 2019): e275–91. https://doi.org/10.1055/s-0039-1695004.

Mandakh, Yumjirmaa, Ralf Rittner, Erin Flanagan, Anna Oudin, Christina Isaxon, Mary Familari, Stefan Rocco Hansson, and Ebba Malmqvist. "Maternal Exposure to Ambient Air Pollution and

Risk of Preeclampsia: A Population-Based Cohort Study in Scania, Sweden." *International Journal of Environmental Research and Public Health* 17, no. 5 (March 7, 2020): 1744. https://doi.org/10.3390/ijerph17051744.

McDuffie, Erin E., Randall V. Martin, Joseph V. Spadaro, Richard Burnett, Steven J. Smith, Patrick O'Rourke, Melanie S. Hammer, et al. "Source Sector and Fuel Contributions to Ambient PM2.5 and Attributable Mortality across Multiple Spatial Scales." *Nature Communications* 12, no. 1 (December 2021): 3594. https://doi.org/10.1038/s41467-021-23853-y.

Mekonnen, Zesemayat K., John W. Oehlert, Brenda Eskenazi, Gary M. Shaw, John R. Balmes, and Amy M. Padula. "The Relationship between Air Pollutants and Maternal Socioeconomic Factors on Preterm Birth in California Urban Counties." *Journal of Exposure Science & Environmental Epidemiology* 31, no. 3 (May 2021): 503–13. https://doi.org/10.1038/s41370-021-00323-7.

Melamed, Nir, Joel G. Ray, Michelle Hladunewich, Brian Cox, and John C. Kingdom. "Gestational Hypertension and Preeclampsia: Are They the Same Disease?" *Journal of Obstetrics and Gynaecology Canada* 36, no. 7 (July 2014): 642–47. https://doi.org/10.1016/S1701-2163(15)30545-4.

Mobasher, Zahra, Muhammad T. Salam, T.Murphy Goodwin, Frederick Lurmann, Sue A. Ingles, and Melissa L. Wilson. "Associations between Ambient Air Pollution and Hypertensive Disorders of Pregnancy." *Environmental Research* 123 (May 2013): 9–16. https://doi.org/10.1016/j.envres.2013.01.006.

Molina Ordas, A, A Rodriguez Gomez, M Heras Benito, Mj Fernandez-Reyes Luis, R Sanchez Hernandez, and F Alvarez-Ude Cotera. "GESTATIONAL HYPERTENSION: RISK FACTORS, CLINICAL AND LABORATORY FINDINGS: PP.32.294." *Journal of Hypertension* 28 (June 2010): e538. https://doi.org/10.1097/01.hjh.0000379832.13474.69.

Mukherjee, Arideep, and Madhoolika Agrawal. "A Global Perspective of Fine Particulate Matter Pollution and Its Health Effects." In *Reviews of Environmental Contamination and Toxicology Volume 244*, edited by Pim de Voogt, 244:5–51. Reviews of Environmental Contamination and Toxicology. Cham: Springer International Publishing, 2017. https://doi.org/10.1007/398_2017_3.

Nobles, Carrie J., Andrew Williams, Marion Ouidir, Seth Sherman, and Pauline Mendola. "Differential Effect of Ambient Air Pollution Exposure on Risk of Gestational Hypertension and Preeclampsia." *Hypertension* 74, no. 2 (August 2019): 384–90. https://doi.org/10.1161/HYPERTENSIONAHA.119.12731.

Pereira, Gavin, Fatima Haggar, Antonia W Shand, Carol Bower, Angus Cook, and Natasha Nassar. "Association between Pre-Eclampsia and Locally Derived Traffic-Related Air Pollution: A Retrospective Cohort Study." *Journal of Epidemiology and Community Health* 67, no. 2 (February 2013): 147–52. https://doi.org/10.1136/jech-2011-200805.

Philip, Sajeev, Randall V. Martin, Aaron van Donkelaar, Jason Wai-Ho Lo, Yuxuan Wang, Dan Chen, Lin Zhang, et al. "Global Chemical Composition of Ambient Fine Particulate Matter for Exposure Assessment." *Environmental Science & Technology* 48, no. 22 (November 18, 2014): 13060–68. https://doi.org/10.1021/es502965b.

Phipps, Elizabeth A., Ravi Thadhani, Thomas Benzing, and S. Ananth Karumanchi. "Pre-Eclampsia: Pathogenesis, Novel Diagnostics and Therapies." *Nature Reviews Nephrology* 15, no. 5 (May 2019): 275–89. https://doi.org/10.1038/s41581-019-0119-6.

Pope, C. Arden, Majid Ezzati, and Douglas W. Dockery. "Fine-Particulate Air Pollution and Life Expectancy in the United States." *New England Journal of Medicine* 360, no. 4 (January 22, 2009): 376–86. https://doi.org/10.1056/NEJMsa0805646.

Possomato-Vieira, J.S., and R.A. Khalil. “Mechanisms of Endothelial Dysfunction in Hypertensive Pregnancy and Preeclampsia.” In *Advances in Pharmacology*, 77:361–431. Elsevier, 2016. https://doi.org/10.1016/bs.apha.2016.04.008.

Raymond, Dahlia, and Erika Peterson. “A Critical Review of Early-Onset and Late-Onset Preeclampsia.” *Obstetrical & Gynecological Survey* 66, no. 8 (August 2011): 497–506. https://doi.org/10.1097/OGX.0b013e3182331028.

Saenen, Nelly D., Karen Vrijens, Bram G. Janssen, Narjes Madhloum, Martien Peusens, Wilfried Gyselaers, Charlotte Vanpoucke, Wouter Lefebvre, Harry A. Roels, and Tim S. Nawrot. “Placental Nitrosative Stress and Exposure to Ambient Air Pollution During Gestation: A Population Study.” *American Journal of Epidemiology* 184, no. 6 (September 15, 2016): 442–49. https://doi.org/10.1093/aje/kww007.

Saenen, Nelly D., Karen Vrijens, Bram G. Janssen, Harry A. Roels, Kristof Y. Neven, Wim Vanden Berghe, Wilfried Gyselaers, et al. “Lower Placental Leptin Promoter Methylation in Association with Fine Particulate Matter Air Pollution during Pregnancy and Placental Nitrosative Stress at Birth in the ENVIR *ON* AGE Cohort.” *Environmental Health Perspectives* 125, no. 2 (February 2017): 262–68. https://doi.org/10.1289/EHP38.

Samet, Jonathan, and second Daniel Krewski. “Health Effects Associated with Exposure to Ambient Air Pollution,” n.d. http://irr.uwaterloo.ca/CQ3Rome/health%20effects.pdf.

Seely, Ellen W., and Jeffrey Ecker. “Chronic Hypertension in Pregnancy.” *Circulation* 129, no. 11 (March 18, 2014): 1254–61. https://doi.org/10.1161/CIRCULATIONAHA.113.003904.

Shaddick, G., M. L. Thomas, P. Mudu, G. Ruggeri, and S. Gumy. “Half the World’s Population Are Exposed to Increasing Air Pollution.” *Npj Climate and Atmospheric Science* 3, no. 1 (December 2020): 23. https://doi.org/10.1038/s41612-020-0124-2.

Shen, Minxue, Graeme N. Smith, Marc Rodger, Ruth Rennicks White, Mark C. Walker, and Shi Wu Wen. "Comparison of Risk Factors and Outcomes of Gestational Hypertension and Pre-Eclampsia." Edited by Sari Helena Räisänen. *PLOS ONE* 12, no. 4 (April 24, 2017): e0175914. https://doi.org/10.1371/journal.pone.0175914.

Shen, Yanling, Guoqi Yu, Cong Liu, Weidong Wang, Haidong Kan, Jun Zhang, and Jing Cai. "Prenatal Exposure to PM $_{2.5}$ and Its Specific Components and Risk of Hypertensive Disorders in Pregnancy: A Nationwide Cohort Study in China." *Environmental Science & Technology* 56, no. 16 (August 16, 2022): 11473–81. https://doi.org/10.1021/acs.est.2c01103.

Sheu, Roger, Tori Hass-Mitchell, Akima Ringsdorf, Thomas Berkemeier, Jo Machesky, Achim Edtbauer, Thomas Klüpfel, et al. "Emerging Investigator Series: Deposited Particles and Human Lung Lining Fluid Are Dynamic, Chemically-Complex Reservoirs Leading to Thirdhand Smoke Emissions and Exposure." *Environmental Science: Atmospheres* 2, no. 5 (2022): 943–63. https://doi.org/10.1039/D1EA00107H.

South Africa, Academy of Science of, Brazilian Academy of Sciences, German National Academy of Sciences Leopoldina, U. S. National Academy of Medicine, and U. S. National Academy of Sciences. "Air Pollution and Health – A Science-Policy Initiative." *Annals of Global Health* 85, no. 1 (December 16, 2019): 140. https://doi.org/10.5334/aogh.2656.

Stieb, David M., Stan Judek, and Richard T. Burnett. "Meta-Analysis of Time-Series Studies of Air Pollution and Mortality: Effects of Gases and Particles and the Influence of Cause of Death, Age, and Season." *Journal of the Air & Waste Management Association* 52, no. 4 (April 2002): 470–84. https://doi.org/10.1080/10473289.2002.10470794.

Stieb, David M., Marc Smith-Doiron, Jeffrey R. Brook, Richard T. Burnett, Tom Dann, Alexandre Mamedov, and Yue Chen. "Air Pollution and Disability Days in Toronto: Results from the

National Population Health Survey." *Environmental Research* 89, no. 3 (July 2002): 210–19. https://doi.org/10.1006/enrs.2002.4373.

Stowell, Jennifer D, Jianzhao Bi, Mohammad Z Al-Hamdan, Hyung Joo Lee, Sang-Mi Lee, Frank Freedman, Patrick L Kinney, and Yang Liu. "Estimating PM $_{2.5}$ in Southern California Using Satellite Data: Factors That Affect Model Performance." *Environmental Research Letters* 15, no. 9 (September 1, 2020): 094004. https://doi.org/10.1088/1748-9326/ab9334.

Sun, Yi, Xia Li, Tarik Benmarhnia, Jiu-Chiuan Chen, Chantal Avila, David A. Sacks, Vicki Chiu, et al. "Exposure to Air Pollutant Mixture and Gestational Diabetes Mellitus in Southern California: Results from Electronic Health Record Data of a Large Pregnancy Cohort." *Environment International* 158 (January 2022): 106888. https://doi.org/10.1016/j.envint.2021.106888.

Thangavel, Prakash, Duckshin Park, and Young-Chul Lee. "Recent Insights into Particulate Matter (PM2.5)-Mediated Toxicity in Humans: An Overview." *International Journal of Environmental Research and Public Health* 19, no. 12 (June 19, 2022): 7511. https://doi.org/10.3390/ijerph19127511.

Tosevska, Anela, Shubhamoy Ghosh, Amit Ganguly, Monica Cappelletti, Suhas G. Kallapur, Matteo Pellegrini, and Sherin U. Devaskar. "Integrated Analysis of an in Vivo Model of Intra-Nasal Exposure to Instilled Air Pollutants Reveals Cell-Type Specific Responses in the Placenta." *Scientific Reports* 12, no. 1 (May 19, 2022): 8438. https://doi.org/10.1038/s41598-022-12340-z.

Turbeville, Hannah R., and Jennifer M. Sasser. "Preeclampsia beyond Pregnancy: Long-Term Consequences for Mother and Child." *American Journal of Physiology-Renal Physiology* 318, no. 6 (June 1, 2020): F1315–26. https://doi.org/10.1152/ajprenal.00071.2020.

Valdés, Ana, Antonella Zanobetti, Jaana I Halonen, Luis Cifuentes, Diego Morata, and Joel Schwartz. "Elemental Concentrations of Ambient Particles and Cause Specific Mortality in Santiago, Chile:

A Time Series Study." *Environmental Health* 11, no. 1 (December 2012): 82. https://doi.org/10.1186/1476-069X-11-82.

Wang, Wei, Xin Xie, Ting Yuan, Yanyan Wang, Fei Zhao, Zhangjian Zhou, and Hao Zhang. "Epidemiological Trends of Maternal Hypertensive Disorders of Pregnancy at the Global, Regional, and National Levels: A Population-based Study." *BMC Pregnancy and Childbirth* 21, no. 1 (December 2021): 364. https://doi.org/10.1186/s12884-021-03809-2.

Wei, Jun, Cai-Xia Liu, Ting-Ting Gong, Qi-Jun Wu, and Lang Wu. "Cigarette Smoking during Pregnancy and Preeclampsia Risk: A Systematic Review and Meta-Analysis of Prospective Studies." *Oncotarget* 6, no. 41 (December 22, 2015): 43667–78. https://doi.org/10.18632/oncotarget.6190.

Weinberg, Clarice R., Min Shi, Olga Basso, Lisa A. DeRoo, Quaker Harmon, Allen J. Wilcox, and Rolv Skjærven. "Season of Conception, Smoking, and Preeclampsia in Norway." *Environmental Health Perspectives* 125, no. 6 (June 23, 2017): 067022. https://doi.org/10.1289/EHP963.

Weldy, Chad S., Yonggang Liu, H. Denny Liggitt, and Michael T. Chin. "In Utero Exposure to Diesel Exhaust Air Pollution Promotes Adverse Intrauterine Conditions, Resulting in Weight Gain, Altered Blood Pressure, and Increased Susceptibility to Heart Failure in Adult Mice." Edited by Michelle L. Block. *PLoS ONE* 9, no. 2 (February 12, 2014): e88582. https://doi.org/10.1371/journal.pone.0088582.

Wellington, K., and Z. D. Mulla. "Seasonal Trend in the Occurrence of Preeclampsia and Eclampsia in Texas." *American Journal of Hypertension* 25, no. 1 (January 1, 2012): 115–19. https://doi.org/10.1038/ajh.2011.173.

Wu, Jun, Cizao Ren, Ralph J. Delfino, Judith Chung, Michelle Wilhelm, and Beate Ritz. "Association between Local Traffic-Generated Air Pollution and Preeclampsia and Preterm Delivery in the

South Coast Air Basin of California." *Environmental Health Perspectives* 117, no. 11 (November 2009): 1773–79. https://doi.org/10.1289/ehp.0800334.

Yamane, Awole. "Https://Bmcpregnancychildbirth.Biomedcentral.Com/Articles/10.1186/S12884-021-03712-w," March 2021.

Yan, Meilin, Nana Liu, Yunfei Fan, Liangkun Ma, and Tianjia Guan. "Associations of Pregnancy Complications with Ambient Air Pollution in China." *Ecotoxicology and Environmental Safety* 241 (August 2022): 113727. https://doi.org/10.1016/j.ecoenv.2022.113727.

Ying, Wendy, Janet M. Catov, and Pamela Ouyang. "Hypertensive Disorders of Pregnancy and Future Maternal Cardiovascular Risk." *Journal of the American Heart Association* 7, no. 17 (September 4, 2018): e009382. https://doi.org/10.1161/JAHA.118.009382.

Yu, Hongbiao, Yangxue Yin, Jiashuo Zhang, and Rong Zhou. "The Impact of Particulate Matter 2.5 on the Risk of Preeclampsia: An Updated Systematic Review and Meta-Analysis." *Environmental Science and Pollution Research* 27, no. 30 (October 2020): 37527–39. https://doi.org/10.1007/s11356-020-10112-8.

Zhu, Yeyi, Cuilin Zhang, Danping Liu, Sandie Ha, Sung Soo Kim, Anna Pollack, and Pauline Mendola. "Ambient Air Pollution and Risk of Gestational Hypertension." *American Journal of Epidemiology* 186, no. 3 (August 1, 2017): 334–43. https://doi.org/10.1093/aje/kwx097.