The Social Determinants of Preeclampsia and Eclampsia

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

in

Epidemiology

School of Public Health
University of Alberta

ABSTRACT

Evidence has been accumulating in recent years showing that social factors have a determining influence on the health of populations. Specifically, in the field of cardiovascular health research, a growing body of evidence has shown robust associations between the social determinants of health (SDOH) and adverse outcomes. A similar pattern of relationship is demonstrated between socioeconomic inequalities and outcome disparities in maternal and neonatal health epidemiology. Within this context, the current study pulls together these areas of research to shed light onto their intersection area with preeclampsia—a hypertensive disease of pregnancy that is responsible for much of maternal and fetal morbidity and mortality worldwide, as well as for future cardiovascular risks for both mother and child.

To answer the overarching question of how the SDOH are associated with preeclampsia, this research bifurcated into two branches comprising: a systematic review and meta-analysis (SRMA), and a population-based analysis of a Pregnancy Birth Cohort in Alberta. For the SRMA, searches were conducted to identify relevant literature in health sciences databases. The PROGRESS-Plus framework, which offers a structured list of a wide breadth of relevant determinants, was used to guide the search. Observational studies that reported measures of association (odds ratio, prevalence, or hazard ratio) between the outcome of interest (preeclampsia or eclampsia) and a SDOH were included. Quality assessment of studies was completed by two independent assessors using adapted versions of the Newcastle-Ottawa Scale. Included studies were described using narrative analysis and visualized using forest plots. Heterogeneity of studies according to SDOH groups was explored using subgroup analyses. Pooling of included studies' effect measures was planned for methodologically-homogeneous studies using the DerSimonian and Laird method of the random-effects inverse-variance approach.

The initial database search yielded 2,453 records, of which 220 were eligible for full-text screening, and 52 publications were included in the systematic review. Social determinants as well as preeclampsia outcome were operationalized differently within the field and between studies, limiting the comparability. Overall, the studies showed a clear positive relationship between preeclampsia and Black race, Native-American race, education, socioeconomic status, and marital status. This review indicates that there is likely an association of certain SDOH with preeclampsia.

The Alberta study of SDOH and their relationship to preeclampsia was conducted using a 2005-2014 retrospective pregnancy and birth cohort established by Alberta Health administrative, de-identified health records. The primary objective was to assess the relationship between SDOH (maternal ethnicity, immigrant status, marital status, urban/rural residence, and social and material deprivation) and preeclampsia. The secondary objective was to assess if maternal and neonatal outcomes were different among high versus low socioeconomic status women with preeclampsia. Data from deliveries of women aged 15-49, who were residents of Alberta at the time of delivery, and who had a live singleton delivery with gestational age longer than 22 weeks were included. Frequencies and percentages of each independent variable, stratified by preeclampsia outcome, were reported with their p-values. Odds ratios (OR) and 95% confidence intervals (CI) were computed in a univariate analysis for each variable; next we examined the association after adjusting for age and parity; and finally after adjusting for pre-existing disease. The generalized estimated equation (GEE) approach was used to account for multiple data points per woman present in the cohort. Potential confounders included in the multivariable model were age, parity, pre-existing hypertension or cardiovascular disease, gestational diabetes mellitus, and prior diagnosis of diabetes mellitus. A final cohort of 473,143 singleton deliveries were included, with an overall preeclampsia prevalence of 1.46%.

Adjusting for age, parity, and pre-existing clinical risk factors, the SDOH that were positively associated with preeclampsia were rural residence (aOR 1.40, 95% CI 1.32-1.48), marital status (aOR 1.15, 95% CI 1.09-1.22), Filipino ethnicity (aOR 1.52 95% CI 1.35-1.72), and material deprivation (Quintile 5: aOR 1.22, 95% CI 1.12-1.33) compared to their low-risk groups. Women of Chinese ethnicity, South Asian ethnicity, as well as women who were immigrants had significantly reduced odds of preeclampsia compared to the general population. Our study informs clinical practitioners of specific at-risk groups and the need for targeted interventions to alleviate inequalities in maternal and fetal health outcomes.

PREFACE

This thesis is an original work by Sapir Fellus. The Alberta Pregnancy and Birth cohort research project of which this thesis is a part received research ethics approval from the Health Research Ethics Board – Health Panel (Study ID Pro00092567).

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. Padma Kaul, for taking me on as her student and for letting me have the space and independence to develop and pave my own way. I appreciate your time and your mentorship throughout this project. A special thank you to my supervisory committee members: to Dr. Radha Chari, who provided her expert input as an Obstetrician/Gynecologist in the conceptualization of this thesis, and to Dr. Maria Ospina, who supported me by providing expert advice on navigating systematic reviews, as well as her warm and encouraging mentorship.

I also want to thank Alberta Health who provided much of the data used in this thesis. By linking administrative health data, researchers are able to diversify their tools in order to make powerful conclusions about the health of communities. The many hours of quiet, yet meticulous work required to link millions of health-related records are much appreciated. Similarly, I extend a sincere thank you to the team at the Canadian VIGOUR Centre, and especially Anamaria Savu and Sunjidatul Islam for providing me assistance with biostatistical analysis of the cohort study. As well, thank you to Dr. Douglas Dover for providing me with feedback on methodological aspects of the cohort study, as well as for being the author of the Health Equity Measurement Framework, which I found helpful in this thesis.

Thank you to my professors at the School of Public Health at the University of Alberta for providing me with excellent epidemiology, biostatistics, and public health foundations on which I built this thesis. The lessons I have learned from you will surely help me be a more informed, critical, and curious learner throughout my career.

Finally, thank you to my family and friends, both in Edmonton and in Ottawa, who encouraged and supported me throughout my degree. I could not have done this without you.

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CHAPTER 1: Introduction

1.1 Social Determinants of Health: Upstream Factors of Population Health Inequalities

Social epidemiology took roots as early as the 19th century, with the idea that social conditions shape the health of a population. Inequalities in mortality among the rich and poor in France,[1] disadvantaged social conditions and typhus in Germany,[2] and lack of sanitation as the major cause of disease in poor areas in England,[3] are some of the early examples of this burgeoning discipline linking social inequalities and disease.[4] Innate in the field's philosophy was the belief that social and cultural elements are upstream factors that shape patterns of health and disease in a population.[5] Whereas downstream factors are more easily studied and available, they are fundamentally influenced by upstream factors. These factors are thought to be the roots of many health inequalities.[5]

The social determinants of health (SDOH) recognize that a person's health or disease is not created in a vacuum, and that a myriad of social and economic factors shape behaviour, stress, availability of resources, and social support, and that these insidiously influence health states. Causal relationships between SDOH and disease involve a complex web of interacting and mediating factors, such that identifying a coherent link is difficult. To conceptualize this, we used a synthesis of evidence-based SDOH frameworks, the recently published Health Equity Measurement Framework (HEMF) by Dover and Belon (Figure 1.1).[6] The authors integrated current literature as well as existing frameworks such as the World Health Organization's Commission on Social Determinants of Health conceptual framework as well as on the Alberta Quality Matrix for Health developed by the Health Quality Council of Alberta, in order to describe key empirical evidence for the causal pathway of the SDOH and health equity using causation and effect modification principles. Central to the HEMF is the *Stress Response*, which the authors describe as a process affecting multiple body systems and causing a biological change such as a rise in hormones and increased immune response. By providing a framework which takes into consideration upstream, midstream, and downstream factors including both individual determinants such as biology and health-related behaviours, as well as societal pre-cursors such as social stratification processes, the HEMF provides a population-level, evidence-based conceptualization of the process moving from SDOH to health states and health outcomes.[6]

According to the HEMF framework, the *Stress Response* which leads to the *Health State* is causally linked by *Psychosocial Stressors*, and the effect of the latter on the *Stress Response* is modified by *Appraisal and Coping*. Psychosocial Stressors in turn are influenced by both *Social Location* and by *Material Circumstances*. *Social Location* is defined by Dover and Belon as the "rank or position an individual is attributed to hold in a sociocultural and economic hierarchy within a society at a given time," and can be measured through indicators of power, (e.g., workplace control and gender roles), resources (e.g., income and social class), prestige (e.g., achievement in education and occupation) discrimination (e.g., immigration status and religion). Thus, individuals who are placed in a lower *Social Location*, for example new immigrants or people in a lower-status occupation, are more likely to be victimized or face discrimination than people in higher tiers of *Social Location*, resulting in higher *Psychosocial Stressors*. *Material Circumstances* refers to the income and material or non-material assets which allow individuals to purchase and consume in order to live in a dignified way as they see fit, and includes basic needs such as housing and food, household amenities, and ability to purchase social goods and services such as education and healthcare. Poor *Material Circumstances*, such as either acute or chronic lack of income, food, or housing, can lead to *Psychosocial Stressors*, which in turn affect the *Stress Response* and exacerbates health.[6]

The HEMF is also corroborated by recent biomedical research linking low socioeconomic status (SES) to major adverse cardiac events mediated through a neurobiological stress response.[7] By measuring arterial inflammation and amygdalar activity, both stress-associated physiological responses, the authors found that those living in lower-SES neighbourhoods had increased new-onset physiological stress changes, and relatively higher rates of CVD events. Together with the HEMF and emerging research about how low SES takes root in the body to produce disease, a question emerged: what relationship can be discerned between SDOH and preeclampsia, a CVD-related disease of pregnancy?

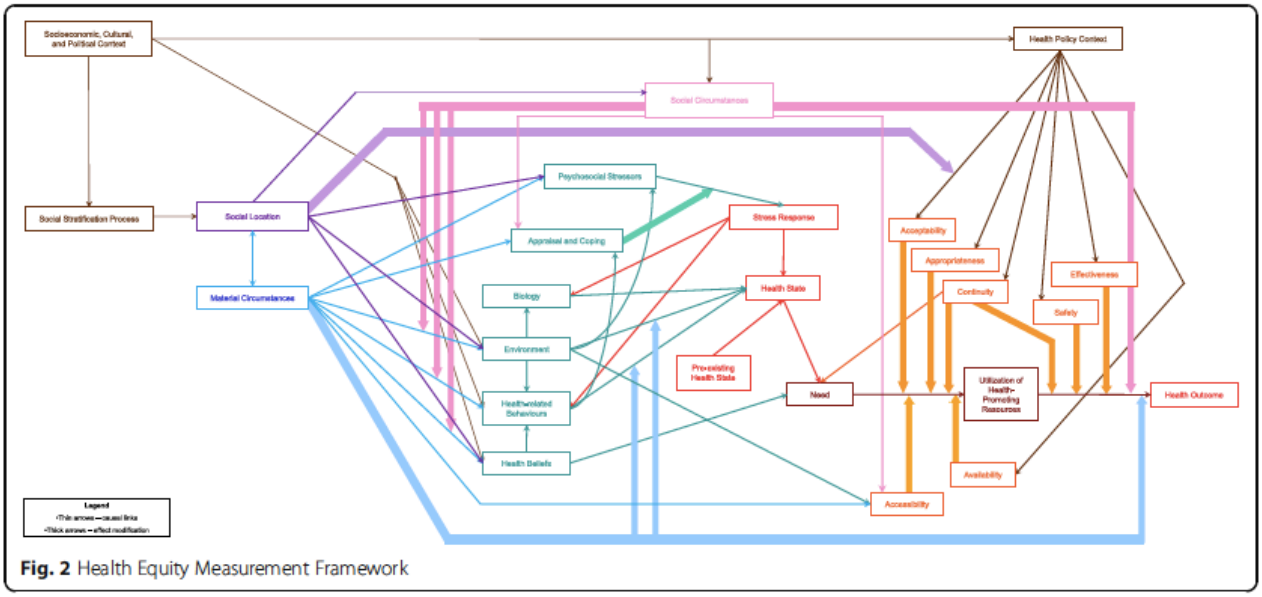

Figure 1.1: Health Equity Measurement Framework. **Thin arrows** – causal links. **Thick arrows** – effect modification. Reprinted with permission from Dover and Belon (2019).[6]

This thesis will use the lens of SDOH to investigate the relationship between several social determinants and preeclampsia. Currently, there is no proposed pathway between inequalities in SDOH and preeclampsia. But this discussion will draw from the HEMF as well as from current literature of how social stress affects the placental environment in order to provide context to our research. Bridging the social realities of the woman with the biological manifestations of disease could provide a more salient and well-defined framework to not only investigate the processes that lead to disease, but also to come up with evidence-based interventions to disrupt or slow down these processes.

1.2 The Mother-Placenta-Fetus Triad and Maternal Social Adversities

The placenta is the organ of pregnancy which is the site of nutrient and waste exchange that allows the fetus to grow. It is believed that preeclampsia is a placental disease, with delivery of the placenta being the only cure.[8] A discussion of risk factors and plausible mechanisms thus ought to include this important, yet often forgotten organ. Although there is much to be discovered about the placenta, it is known that placental metabolism changes in response to changing maternal environment. One model to explain how the placenta is modulated during pregnancy is the *placental nutrient sensing model*, where the placental syncytiotrophoblasts, the site of

communication between fetal and maternal tissues, sense changes in maternal signals, and lead to a corresponding placental response which modulates fetal growth.[9,10] Not only is the placenta thought to detect and respond locally to maternal signals such as hypoxia, toxins, changed nutrition and stress, but the placenta reciprocally secretes hormones and factors, such as inflammatory factors, into the maternal system. These placental factors, including angiogenic factors, cytokines, and inflammatory factors, are secreted to the mother's bloodstream, where systemic changes occur.[11] Thus, the placental-utero-maternal triad is a communicating microcosm that have complex physiologic relationships.

A paper by Thornburg et al. brought forward a theoretical framework of how social determinants of a pregnant woman's environment may alter and affect placental growth and function.[12] More specifically, the authors discussed how maternal social adversities may lead to epigenetic changes which affect placental health, which in turn manifest in insidious placental disease affecting fetal growth and disease risk. These authors propose three social factors that may affect the placenta, and subsequently may offer an understanding to the developmental origins of disease: social stress, malnutrition during pregnancy, and environmental toxins (see Figure 1.2).[12] Each of these maternal social stressors may have an individual effect on placental changes during pregnancy, but can also be present in conjunction with each other and lead to a multiplicity of effects during pregnancy and beyond.

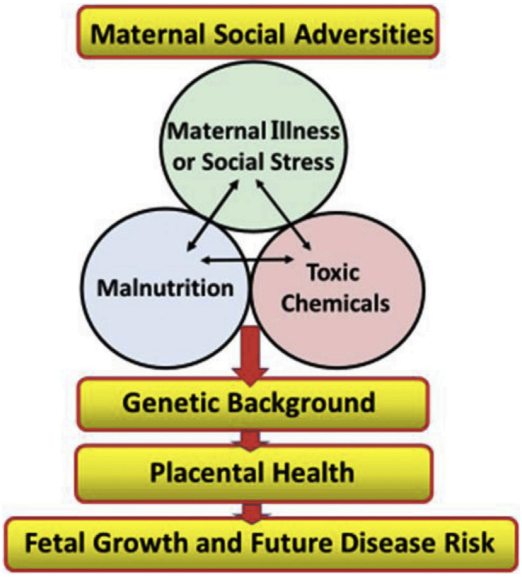

Figure 1.2: Maternal social adversities act through stressors, including social stress, illness, poor nutrition, and toxic chemicals, that detrimentally affect placental health in accordance with epigenetic drivers and genetic predispositions. Robust fetal growth and unfettered organ

development depend on a well-constructed and healthy placenta that is able to perform optimal transport, endocrine, and gas exchange functions. Reprinted with permission from Thornburg, Boone-Hinonen, and Valent (2020).[12]

A mother's experience during pregnancy, which is inextricably linked to her experience of life leading up to her pregnancy, can hence impart upon her child a transgenerational, physical effect, through the placenta. Several studies have evaluated the impact of stress, either during childhood or adulthood, on fetal outcomes. Women who underwent acute stressful periods during pregnancy, such as natural disasters or other devastations such as September 11th, were found to have low-birthweight babies, or babies with hormonal dysregulation manifested as increased adiposity in childhood.[13,14] A systematic review on pregnancy outcomes among women who experienced domestic violence before pregnancy, an experience which may lead to many episodes of acute stress, found increased odds of preterm birth and low birth weight.[15] The underlying mechanism through which stress affects maternal and fetal health during pregnancy is yet unclear, as hormonal levels are modulated by the maternal, fetal, and placental neuroendocrine contributions. It has been posited, however, that chronic maternal stress leads to excess release of corticotropin releasing hormone (CRH), a placentally-derived hormone which has established links with adverse birth outcomes such as preterm delivery.[16,17]

Another mechanism by which a woman's external social environment can affect the placenta may be intrinsically linked with poor nutrition which often coincides with low SES.[12] Normal fetal weight gain is favoured when women have better nutritional profiles before, as well as during, pregnancy.[18] This suggests that periods of malnutrition affect placental health, and through it, the baby's health. Populations that are food-insecure, or where a nutritious diet is harder to obtain, can experience increased risks during pregnancy as a result. In the same vein, lower SES groups are more likely to consume fast foods which are associated with greater inflammatory potential,[19] a factor which is associated with preeclampsia through the systemic inflammatory endothelial response.[8] The food insecurity as well as lack of access to wholesome foods can be one manifestation of how social factors can 'get under the skin', through the placenta, and affect a woman's CVD and preeclampsia risk.

Thornburg et al. suggests that low social status can also be associated with toxic chemicals present in the mother's environment, which in turn make their way to the placenta.[12] Indeed, research has shown that toxicants such as arsenics and polycyclic aromatic hydrocarbons, found

in highly industrialized and polluted areas, are associated with low SES.[20] Further, a case-control study has found that placentas of women with preterm deliveries showed evidence of oxidative stress induced by lead exposure, compared to women with normal pregnancies.[21] In another study, toxicants such as mercury, lead, and selenium were found in placental tissue, suggesting these potentially harmful materials cross the placental barrier, although only mercury was associated with preterm or low birthweight deliveries.[22]

Other than the toxic chemical exposure being more prevalent in low SES neighbourhoods, it has also been brought forth that the stress of living in poor neighbourhoods can in itself be considered toxic. Evidence shows persistent inequalities in pregnancy outcomes by area-level indicators such as poverty and violence.[23-26] The previously mentioned study examining how the stress response was activated in individuals living in lower SES neighbourhoods, which showed these individuals have a higher odds of adverse cardiac outcomes than individuals in higher SES neighbourhoods, supports the hypothesis that where one lives inculcates potentially harmful physiological changes.[7]

Social stress can be conceptualized as an insidious form of stress that takes root physiologically in the body over longer periods of time.[12] Included in the realm of social stressors, it has been posited that the experience of racism—whether through chronic experiences such as the daily hassles of interpersonal disrespect and strife encountered over a lifetime, or more acute episodes of discrimination such as violence—sets in motion a series of stress pathways.

However, to highlight the difference between race and racism, it is also important to look at the how the experience of racism affects a woman's health during pregnancy. In one particular study, lifetime racism experienced by African-American women interacted with increased diastolic blood pressure (DBP) to predict low birthweight and preterm birth.[27] In other words, increased DBP among African-American women was predictive of adverse birth outcomes if women reported high levels of experienced racism. The link between race and adverse health outcomes has also been shown in epidemiological CVD studies in the U.S. In one particular study, Lukachko and colleagues investigated how structural racism levels, as operationalized by political participation, employment, education, and judicial treatment, were associated with myocardial infarction (MI) risks within Black and White populations in different states. They found that Blacks living in states with increased structural racism had higher rates of MI than Blacks living in less racist states, while this observation was not found among Whites.[28] Considering that

preeclampsia is a hypertensive disease of pregnancy, tightly linked with CVD, this study is compelling and might show on a bigger scale how insidious processes such as racism can translate into cardiac pathologies, throughout a woman's life cycle.

The placenta is the conduit between the mother and child, and so it is suggested that the placenta is the mediator through which low SES and high social stressors such as poverty, racism, and lack of access to good nutrition, affect the child. If this is observed for neonatal health outcomes, then perhaps SDOH affect the placenta in other ways, as well, namely by increasing risk to preeclampsia.

Within this framework of SDOH described in this introductory chapter (Chapter 1), the objectives of my Master's research project were to: 1) conduct a systematic review of the relationship between SDOH and preeclampsia (Chapter 2); 2) use a unique population-level Pregnancy Birth Cohort in Alberta to examine differences in preeclampsia occurrence across several SDOH such as ethnicity, neighbourhood-level SES, rural residence, marital status, and immigrant status (Chapter 3); 3) summarize the findings of the two individual studies and suggest future directions for this research (Chapter 4).

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CHAPTER 2: Systematic Review and Meta-analysis of the Social Determinants of Preeclampsia

2.1 Introduction

Preeclampsia is a disease of pregnancy characterized by increased hypertension and proteinuria, or other signs of end-organ damage.[1] The disease is a major cause of morbidity and mortality among pregnant women around the world, with a prevalence of approximately 3-8% in industrialized countries.[2] In lower to middle-income countries, preeclampsia and its exacerbated form, eclampsia, are responsible for 10-15% of maternal deaths.[3] Consequences for both the neonate and the mother can be dire, both in the short- and long-term after a pregnancy complicated by preeclampsia. Neonatal adverse outcomes include low birth weight, fetal growth restriction, and oligohydramnios,[4] as well as later-life susceptibility to chronic disease such as hypertension.[5] Preeclampsia is responsible for increased risk of fetal and neonatal death compared to normotensive pregnancies.[4,6] Other than the immediate life-threatening risk of preeclampsia, a systematic review and meta-analysis found that women with a history of preeclampsia have increased future risk of hypertension, ischaemic heart disease, stroke, and venous thromboembolism.[7] Although the underlying mechanism is unclear, evidence suggests that preeclampsia is a systemic response to pregnancy, involving endothelial damage that may be the impetus of future cardiovascular risk.[8] Given the disease's far-reaching effects, identifying at-risk populations and providing prophylactic care can have the potential to reduce maternal and neonatal morbidity, as well as health care costs.

Preeclampsia incidence has mostly been attributed to biological differences in women, and hypotheses are buttressed upon large-scale studies showing women with preeclampsia demonstrate signs of increased oxidative stress, genetic and immunologic factors, and other molecular markers.[8] However, an explanation of why these biological pathways are catalyzed in some women and not others is still unclear. Departing from a biomedical framework, the biopsychosocial paradigm of the social determinants of health (SDOH) contends that individual health is determined in interactive contexts, and that health states are a result of multilevel interactions between social and biological factors.[9] Indeed, recent advances in cardiovascular disease (CVD) research have shown that poor socioeconomic status is inversely related with adverse CVD outcomes.[10-12] Given the inextricable relationship between preeclampsia and cardiovascular health, it is expected that social and economic deprivation would exhibit similar patterns in this

disease of pregnancy. Epidemiological investigations of more upstream causes that may influence a woman's risk towards hypertensive disease aim to complement advances in etiological and clinical research.

For this reason, we have conducted a systematic review and meta-analysis of population-based evidence of the SDOH and their relationship with preeclampsia and eclampsia (henceforth referred to as preeclampsia) occurrence. Our rationale is threefold: Elucidating the impact of social determinants on preeclampsia can 1) complement biopsychosocial understanding of preeclampsia by providing evidence of which upstream social and contextual factors lead to disease, 2) contribute to the growing body of evidence demonstrating the link between socioeconomic health inequalities and adverse pregnancy health outcomes; and 3) identify demographic and social risk factors that may guide healthcare workers and health system services in more targeted prevention and surveillance. We hypothesize that through synthesizing the available evidence, we will be able to detect higher prevalence of preeclampsia among women who are comparatively more socially and economically disadvantaged.

2.2 Methods

2.2.1 Searches

This was a systematic review and meta-analysis of preeclampsia and eclampsia distribution by SDOH. The study followed principles of the Meta-Analyses Of Observational Studies in Epidemiology (MOOSE)[13] in order to apply a structured protocol in formulating the research question, data collection, and reporting of results (see MOOSE checklist in Appendix 1). The study protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number CRD42019140087). The methods and specific keywords for each database were developed by the first author with the guidance of a Health Sciences librarian (JK) at the University of Alberta.

Searches to identify relevant literature were conducted from database inception until June 2019 in the following electronic databases: Ovid Medline, Ovid Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Sociological Abstracts. To identify and categorize relevant SDOH, we used the PROGRESS-Plus framework, which is a collection of socially stratifying factors driving differences in health outcomes, proposed by Evan and Brown in 2003,[14] and endorsed by Campbell and Cochrane Equity Methods Group in 2012.[15] The framework includes place of residence, race/ethnicity/culture/language, occupation, gender/sex,

religion, education, socioeconomic status, social capital, and "plus" (i.e. other personal characteristics such as parents' education or smoking status, age, and disability).[14] In this review, the words 'race' and 'ethnicity' were used interchangeably to express the complex construct of sociocultural identity, and reflect vernacular used in included papers. The search terms were exploded to capture keywords related to the subject heading. Search terms aimed to agglomerate the outcome of interest in its variant spellings in conjunction with the SDOH (see Appendix 2 for specific keywords and Medical Subject Heading terms). In order to avoid introducing selection bias, no restriction was applied based on publication type (including abstracts and conference proceedings), year, or language of publication. Records that were written in languages other than English were translated using online text translators in order to determine relevance to the study objectives.

2.2.2 Study Selection

Titles and abstracts of papers resulting from the search were screened blindly by two independent reviewers (SF and LB). Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) was used to facilitate the initial screening process. Full-text papers of relevant studies, or of records without sufficient information in their title or abstracts, were obtained for full-text review. If studies could not be located in the local library's catalogs, interlibrary loan services were elicited. Studies were included if they were primary observational research (i.e. study was cohort, cross-sectional, or ecological in its design.), the population of interest was pregnant women, at least one of the main exposures of interest was a SDOH as outlined by the PROGRESS-Plus framework, a comparison group without the social determinant of interest was assessed, and if at least one of the outcomes reported was preeclampsia or eclampsia incidence or prevalence. Case-control studies were excluded because this study design does provide unbiased information on the prevalence of the long-term exposures of interest in our review. Studies that reported preeclampsia outcome in the same group as other hypertensive disorders such as gestational hypertension were excluded because preeclampsia is considered a distinct disease with its own epidemiology, pathophysiology, risk factors, and consequences.[16-18] The inclusion/ exclusion form can be found in Appendix 3.

2.2.3 Data Extraction

Data extracted from each study were the following: general information (title, authors, year of publication, country, setting), study design (prospective cohort, retrospective cohort, cross-sectional, ecological), number of participants, study population characteristics (maternal age, gestational age, co-morbidities, selection criteria), exposure of interest (SDOH examined, measurement methods), confounders if estimates were adjusted, and study outcomes (odds ratios [ORs], rate ratios [RRs], measures of variability, as well as raw group numbers if available). Authors were contacted if clarification was needed for data extraction. Clarification was elicited in the data extraction phase from the main contact of the study by Booker et al.[19] regarding the comparison group used to assess preeclampsia rates among Black women. Study populations were defined as either high risk-set (e.g. studies restricted to women with adolescent pregnancies, advanced maternal age, multiple pregnancies, and women with pre-existing conditions) or low risk-set (e.g. studies restricted to women with no pre-existing conditions and singleton deliveries). The first author (SF) extracted data from included studies, and a second reviewer (LB) independently reviewed the data for accuracy and completion.

2.2.4 Methodological Quality Assessment

Overall study quality was assessed independently and blindly by two reviewers (SF and BM) using adapted versions of the Newcastle-Ottawa Scale (NOS). This quality assessment tool is one of the tools recommended for assessment of observational studies in systematic reviews.[20] The NOS for cohort studies was used to assess cohort and ecological studies.[21] A version of the NOS to assess quality and risk of bias in cross-sectional studies was adapted from a systematic review by Herzog et al.[22] Each study was assessed through a star-point system in the three broad categories of selection, comparability, and outcome/exposure. The overall numeric scores were then converted to a score of overall quality: ‘good’ ‘fair’ or ‘poor’ (see Appendix 4 for NOS tools and conversion ranges of scores).

Although defined as a quality assessment tool, the NOS contains elements of risk of bias and was thus deemed acceptable for an overall quality and risk assessment tool. Specifically, selection bias was assessed by rewarding stars to a study if the exposed and unexposed groups were pulled from the same base population, and if efforts to limit and explain missing data due to loss to follow up were evident; internal validity was assessed through awarding points to studies using valid methodology for exposure and outcome ascertainment, such as through the use of

administrative records; confounding was assessed in the 'comparability' section of the tool, where studies were rewarded points for taking into consideration important confounders such as gestational age, maternal age, and comorbidities.

Study selection, recording of extracted data, and quality assessment were managed using Microsoft Excel (Microsoft Corporation, Redmond, WA). Any disagreements between reviewers regarding inclusion, data extraction, or quality assessment were resolved through discussion and consensus.

2.2.5 Data analysis

Included studies were described using a narrative synthesis, and general characteristics (year, country, description of population, SDOH, outcome of interest and how these were measured) were summarized in evidence tables. For each SDOH, forest plots depicting individual effect estimates (crude ORs) for preeclampsia were constructed.

Meta-analyses were conducted for sufficiently homogeneous studies (I-squared values <50%) that evaluated similar social determinants of preeclampsia among similar populations (e.g., same country, similar risk-set of base population as described above), and using similar outcome definitions. Pooled estimates were synthesized using the DerSimonian and Laird method of the random-effects inverse-variance approach to meta-analysis because of the likely heterogeneity of predictors, as well as the variability in the studies' contexts.[23,24] When pooling was appropriate, a pooled estimate was additionally displayed using the summary diamond in separate figures.

Heterogeneity of studies was assessed using the I-squared statistic with low, moderate, and high degrees of heterogeneity corresponding to I-squared values of 25, 50, and 75%, respectively.[25,26] High heterogeneity was explored using subgroup analysis, such as through assessing studies according to population characteristics (i.e. geographical location, singletons vs. multiple births, presence of comorbidities), study operationalization of exposure variables, or clinical definition of preeclampsia outcome.[23] As laid out in the Cochrane Handbook for Systematic Reviews of Interventions, reliable conclusions will only be reported if subgroup analyses were pre-specified in the methods section, so the aim of exploring heterogeneity will be to generate hypotheses, and not to draw conclusions.[23] All effect estimates were reported as the OR or RR and their 95% confidence interval (CI). Statistical pooling and forest plot visualization

were conducted using Review Manager (RevMan) software version 5.3 (Copenhagen: The Nordic Cochrane Centre; The Cochrane Collaboration 2014).

2.3 Results

Figure 2.1 provides a detailed outline of the inclusion/exclusion process of the systematic literature search. The search strategy yielded a total of 2,453 records. After removal of 663 duplicates, the titles and abstracts of 1,790 records were screened for study relevance. The full text of 220 studies were retrieved for assessing study eligibility and finally 52 studies were selected for inclusion in the review. The list of references of the 168 excluded studies, by reason for exclusion, is available in Appendix 5.

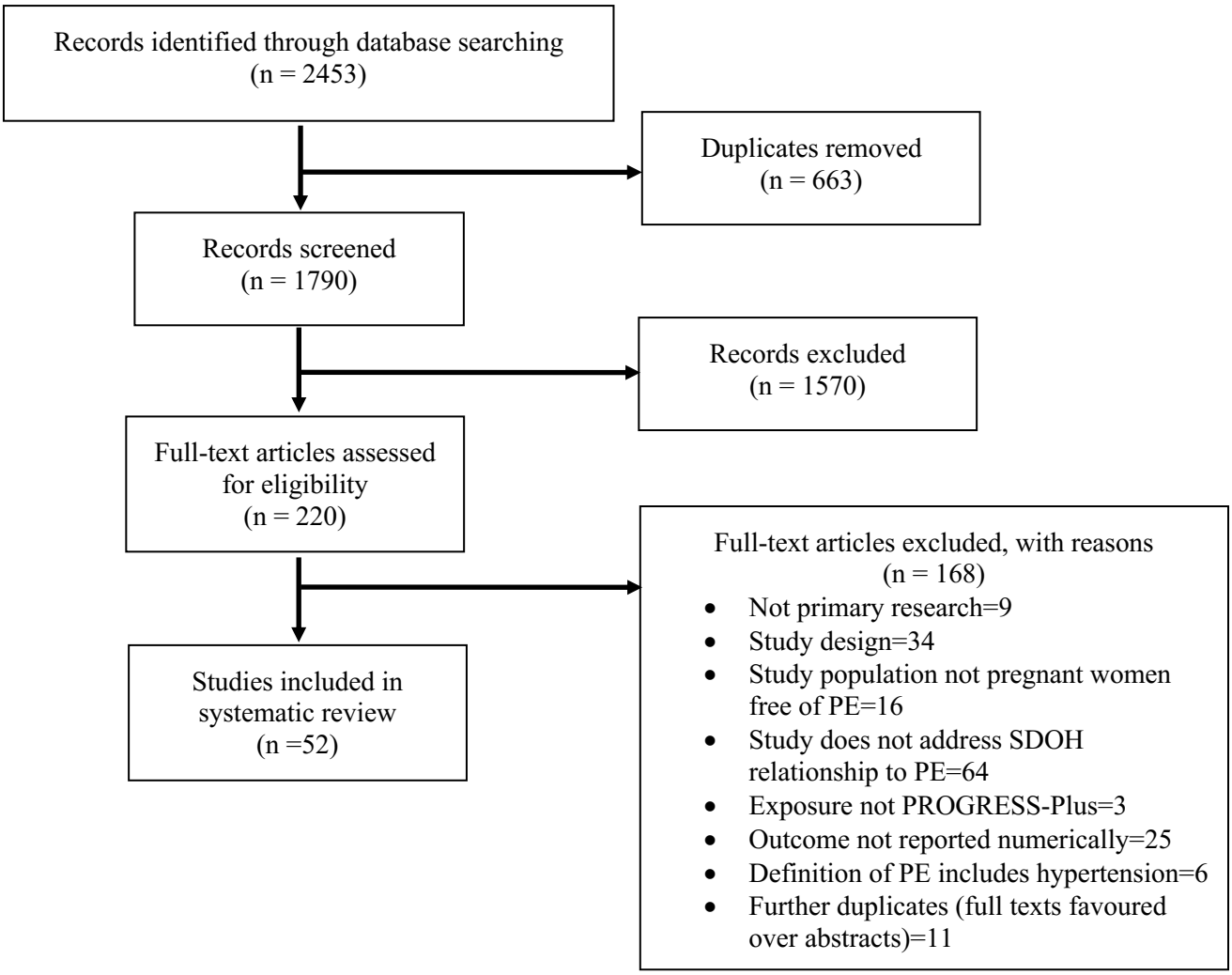


Figure 2.1: Flow diagram of study selection according to MOOSE guidelines[13]

2.3.1 Characteristics of included studies

Overall, 19 countries were represented in the 52 studies included in the review, including United States (U.S.),[19,27-47] Netherlands,[48-52] Norway,[53-55] United Kingdom (U.K.),[56,57] France,[58,59] Greece,[60,61] Sweden,[62,63] Ethiopia,[64] Israel,[65] Germany,[66] New Zealand,[67] China,[68] Turkey,[69] Chile,[70] Korea,[71] Canada,[72] Spain,[73] Ireland,[74] Saudi-Arabia,[75] and Ethiopia,[64] as well as two cross-country studies.[76,77] The median publication year was 2013 (interquartile range=eight years). The years of study span from 1969 to 2016, with an average follow-up time of seven years. In terms of study design, there were eight prospective cohort studies,[33,41,48-50,52,54,58] 38 retrospective cohort studies[19,27-32,34-40,42-47,51,53,55-57,59-62,65-67,71,73,74,77,78], five cross sectional studies,[64,69,70,75,76] and one ecological stuy.[68]

Studies differed in regard to the risk profile of the populations of interest. Eleven studies specifically excluded pregnancies of women with various pre-existing conditions (e.g., hypertension, pre-existing diabetes mellitus [DM], gestational diabetes mellitus [GDM], renal abnormalities);[37,38,41,44,46,50,52,54,66,68,79] 4 studies had a higher-risk population of women with either DM,[31] GDM,[35,59] or chronic hypertension;[39] one study chose a teenaged population,[36] one study restricted the study to women aged 40 years or above,[19] one assessed a population with varying degrees of obesity,[34] and another analyzed a population of twin gestations.[32]

The studies included 91 relationships linking preeclampsia to the following social determinants of health: rural residence (N=1)[78], Black race (N=18),[19,28-32,34-36,38-40,43-46,52,57] Hispanic ethnicity (N=14),[28-32,35,36,39-41,43-46] Asian race (N=14),[28,30-32,35-37,39,40,45,47,52,57,67] Native race (N=6),[28,32,42,45,47,67] other race/ethnicities (N=4)[44,47,50,56], employment status (N=4),[33,51,66,75] religion (N=1),[61] education (N=7),[27,31,48,55,62,64,76] socioeconomic status (N=8)[46,49,54,63,67,68,71,73] and social capital which was subcategorized into marital status (N=3)[27,64,76] immigrant/refugee status (N=8),[53,55,60,65,66,69,70,77] and other measures of social deprivation (N=3).[58,59,74] Detailed characteristics of the studies are presented in Table 2.1.

In terms of the outcome variables of interest and their definitions, studies fell into 9 different categories of definition, as presented in Table 2.2. Eighteen studies assessed preeclampsia outcome as hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation) combined with proteinuria;[41,48-51,53-57,59,60,63,64,68,73,76,78] two studies used the outdated definition of preeclampsia of hypertension (diastolic blood pressure ≥90 mmHg) and proteinuria;[52,74] three studies utilized the expanded definition of preeclampsia

recommended in 2013 by the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy[80] which includes not only proteinuria but also other signs of end-organ damage or hemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome;[61,66,67] three studies assessed eclampsia outcome;[28,76,78] four studies combined preeclampsia and eclampsia into a single outcome variable;[27,38,42,44] eight studies included all forms of preeclampsia or eclampsia, in addition to chronic hypertension superimposed by preeclampsia;[29-31,43,46,47,62,77] one study considered early and late-onset preeclampsia;[27] and one study assessed severe preeclampsia, defined as any gestational hypertensive disease type treated with $MgSO_4$.[71] Fifteen studies did not specify in their methodologies how the outcome was operationalized or diagnosed.[19,32-37,39,40,45,58,65,69,70,75]

Table 2.1: Characteristics of the 52 studies included in the systematic review of the relationship between social determinants of health (SDOH) and preeclampsia.

Study by SDOH and quality assessment score	Study Design and country	Study Population	SDOH and comparison groups
Place of residence			
Lisonkova 2016 *Good*	Retrospective cohort Canada	All mothers who gave birth in British Columbia, Canada (>99% of deliveries of province) between 2005-2010	▪ Rural vs. Urban residence
Race/ethnicity			
Anderson 2012 *Good*	Retrospective cohort New Zealand	Singleton pregnancies, excluding congenital abnormalities, delivered at a tertiary referral service at Auckland, New Zealand, between 2006-2009	▪ Ethnicity (European, Maori, Pacific, Chinese, Indian, Other Asian, Other)
Booker 2018 *Poor*	Retrospective cohort United States	Women of advanced maternal age (aged 40-54). Sample includes about 20% of all U.S. hospitalized deliveries, between 1998-2014	▪ Ethnicity (Black vs. non-Black)
Bouthoorn 2012 *Good*	Prospective cohort Netherlands	Generation R Study women who had singleton deliveries, without pre-existing hypertension, between 2002-2006.	▪ Ethnicity (Dutch, Turkish, Moroccan, Antillean, Surinamese, and Cape Verdean)

Brown 2007 *Good*	Retrospective cohort United States	Women aged 11 or older with Medicaid insurance who delivered at a tertiary care delivery hospital in Durham, NC, between 1994-2004.	▪ Race (Hispanic, African American, White)
Caughey 2005 *Good*	Retrospective cohort United States	Nondiabetic, non-hypertensive women belonging to the ethnicities of interest (White, African American, Hispanic, Native American, and Asian) who gave birth to a singleton in Northern California between 1995-1999.	▪ Ethnicity (Asian, African American, Hispanic, White, and Native American)
Farrar 2018 *Fair*	Retrospective cohort United Kingdom	British and Pakistani women, excluding women with pre-existing hypertension and multiple pregnancies between 2007-2011	▪ Ethnicity (White British vs. Pakistani)
Fong 2013 *Fair*	Retrospective cohort United States	Deliveries in California State of women aged 15-55 between 2001-2007	▪ Race (Caucasian, Black, Hispanic, Native American, Asian/Pacific Islander)
Ghosh 2014 *Good*	Retrospective cohort United States	Nulliparous women with singleton pregnancies from 12 clinical centres across the country between 2002-2008	▪ Race (non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Pacific Islander, multiracial/other)
Gong 2012 *Good*	Retrospective cohort United States	Women with live singleton births >20 weeks of gestation, without pre-existing chronic hypertension, diabetes, renal disease, or pregestational diabetes, from New York City between 1995-2003.	▪ Ethnicity (according to 13 different ethnic groups, the largest ones being Non-Hispanic Whites, African American, East Asian, Hispanic Caribbean, non-Hispanic Caribbean, South American)
James-Todd 2014 *Good*	Retrospective cohort United States	Women diagnosed with pre-existing diabetes and who gave birth to a singleton in the State of New York between 1995-2003	▪ Ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, East-Asian, South-Asian)

Kernberg 2018 *Poor*	Retrospective cohort United States	Nulliparous twin gestations in California, U.S.	▪ Race (White, Black, Hispanic, Asian, Native American)
Khalil 2013 *Good*	Retrospective cohort United Kingdom	Singleton deliveries of women attending their first prenatal visit (at 11 to 19th week of gestation), excluding fetal aneuploidies or major defects, and pregnancies terminated for psychosocial reasons	▪ Ethnicity (Afro-Caribbean, South-Asian, East-Asian, Mixed)
Knuist 1998 *Fair*	Prospective cohort Netherlands	Nulliparous women with singleton pregnancies registered for prenatal care before 20 weeks and delivering after 24 weeks of gestation, without pre-existing disease (diabetes, hypertension, and renal abnormality), between 1992-1994	▪ Ethnicity (White, Mediterranean, Asian, Black, Other). Assessed ethnicity as countries of origin.
Marshall 2014 *Good*	Retrospective cohort United States	Singleton deliveries born to obese Black or White Missouri residents, between 2000-2006 *High-risk women were excluded (hypertension, diabetes, pregnancies with congenital anomalies)	▪ Ethnicity (African American vs. Caucasian)
Nakagawa 2016 *Good*	Retrospective cohort United States	Women who are residents of Hawaii, aged >16, hospitalized for a delivery, between 1995-2013	▪ Ethnicity (Chinese, Filipino, Japanese, Native Hawaiian, other Asian, other Pacific Islanders, Other, White)
Nguyen 2012 *Good*	Retrospective cohort United States	Singleton pregnancies with gestational diabetes mellitus in California (women with diabetes 1 and 2 were excluded), in 2006	▪ Race (White, Black, Hispanic/Latin, Asian)
Penfield 2013 *Fair*	Retrospective cohort United States	Live singleton births of nulliparous teenaged women (aged 12-19) who delivered at University of California San Francisco Medical Center, between 1988-2008	▪ Ethnicity (White, African American, Latina, Asian)

Rao 2006 *Fair*	Retrospective cohort United States	All Asian (Japanese, Chinese, and Filipino) women who delivered at the University of California, San Francisco, between 1985-2001	▪ Ethnicity (Japanese, Chinese, Filipino)
Ross 2019 *Good*	Retrospective cohort United States	Singleton births to White or Black women without pre-existing hypertension in California, between 2007-2012	▪ Race (White vs. Black)
Sabol 2014 *Good*	Retrospective cohort United States	California residents with chronic hypertension who delivered live, singleton, non-anomalous neonates between 2005-2008	▪ Ethnicity (White, African American, Hispanic, Asian)
Shen 2005 *Good*	Retrospective cohort United States	Women aged 13-55 who gave birth in U.S. community hospitals between 1998-1999	▪ Ethnicity (White, African American, Hispanic, Asian)
Tanaka 2007 *Fair*	Retrospective cohort United States	Women aged 15-54 without HIV/AIDS residing in New York State who delivered a live neonate between 1993-2002	▪ Race (Hispanic, White, Black, Other)
Wolf 2004 *Good*	Prospective cohort United States	Nulliparous, normotensive, non-proteinuric Hispanic and non-Hispanic Caucasian women who received prenatal care in Massachusetts General Hospital between 1998-2002	▪ Race (Hispanic vs. Caucasian)
Zamora-Kapoor 2016 *Good*	Retrospective cohort United States	Singleton live births to randomly selected first-time mothers of American-Indian/Alaska Native (AI/AN) ethnicity in Washington State, with a frequency-matched sample of White women included as a comparison group, between 2003-2013	▪ Ethnicity (American-Indian/Alaska Native vs. White)
Zhang 2013 *Good*	Retrospective cohort United States	Singleton deliveries to Medicaid recipients in 14 southern states between 2006-2007	▪ Ethnicity (White, African-American, Hispanic)
Occupation/employment			
El-Gilany 2008 *Fair*	Retrospective cohort Saudi-Arabia	Highly educated (secondary school and above) Saudi women who gave birth to live neonate	▪ Occupation (housewives vs. employed)

		in an urban primary health centre in 2006	
Jansen 2010 *Good*	Retrospective cohort Netherlands	Generation R Study women (city of Rotterdam study) who consented to the study, and who had singleton deliveries between 2002-2006	▪ Employment (employed vs. housewife, job-seeking, receiving disability benefit, student)
Magann 1995 *Poor*	Prospective cohort United States	Deliveries of dependent wives of active-duty service men during a 1.5-year period	▪ Employment status
Schneider 2011 *Good*	Retrospective cohort Germany	All women who delivered in Germany in 2006 without diabetes mellitus	▪ Occupation (unskilled worker, skilled worker, management, trainee/student, housewife
Religion			
Anastasiadis 2007 *Fair*	Retrospective cohort Greece	All women who delivered a live or stillbirth infant in one tertiary clinic in a rural territory in Thrace, Greece, between 1986-1999	▪ Religion (Muslim vs. Christian Orthodox)
Education			
Bilano 2014 *Good*	Cross Sectional 23 developing countries in Africa, Latin America and Asia	All pregnant women admitted for delivery in the study's participating hospital centres in developing countries, between 2004-2005 (Africa and Latin America) and 2006-2007 (Asia)	▪ Education
Heshmati 2013 *Good*	Retrospective cohort Sweden	Swedish-born women delivering a live singleton birth in Sweden between 1982-2008	▪ Education
James-Todd 2014 *Good*	Retrospective cohort United States	Women diagnosed with pre-existing diabetes and who gave birth to a singleton in the State of New York between 1995-2003	▪ Education
Lisonkova 2013	Retrospective cohort	Singleton deliveries in Washington State between 2003-2008.	▪ Education (less than high school vs. high school and more)

Good	United States		
Silva 2008 *Good*	Prospective cohort Netherlands	Generation R Study women (city of Rotterdam study) who consented to the study, and who had singleton deliveries excluding abortions or fetal death before 20 weeks, between 2002-2006	▪ Education (as indicator of maternal socioeconomic status)
Sole 2018 *Good*	Retrospective cohort Norway	Singleton pregnancies without any major congenital abnormalities, between 1999-2014	▪ Education
Tessema 2015 *Poor*	Cross Sectional Ethiopia	Hospital-based pregnant women who attended antenatal care, with gestational age greater than 20 weeks in 2013	▪ Education (unable to read/write, able to read/write, primary, secondary, tertiary schooling)
Socioeconomic status			
Anderson 2012 *Good*	Retrospective cohort New Zealand	Singleton pregnancies, excluding congenital abnormalities, delivered at a tertiary referral service at Auckland, New Zealand, between 2006-2009	▪ Neighbourhood-level socioeconomic status (inequality measured by neighbourhood income quintiles)
Choe 2016 *Good*	Retrospective cohort Korea	Stratified random sample of Korean women aged 15-44 according to gender, age group, and income level, between 2002-2013.	▪ Individual-level socioeconomic status (measured by household income inequality)
Clausen 2006 *Good*	Prospective cohort Norway	Women without type I diabetes of Norwegian ancestry living in Oslo, recruited to study, and who delivered a singleton not ending in abortion, between 1994-1996	▪ Neighbourhood-level socioeconomic status (Oslo West high wealth vs. Oslo East low wealth)
Gudmundsson 1997 *Poor*	Retrospective cohort Sweden	Women delivering in one hospital in the city of Malmö between 1990-1993	▪ Neighbourhood-level socioeconomic status (defined as immigrant population percentage, median income, percentage of population on welfare)

Larroca 2017 *Good*	Retrospective cohort Spain	All women with singleton births who delivered at a Madrid General Hospital, between 2010-2016	▪ Socioeconomic status (defined as maternal country of origin's Human Development Index (HDI); 3 categories: very high, high, and medium/low)
Tanaka 2007 *Fair*	Retrospective cohort United States	Women aged 15-54 without HIV/AIDS residing in New York State who delivered a live neonate between 1993-2002	▪ Socioeconomic status (neighbourhood poverty level as the percentage of residents living below the poverty line)
Timmermans 2011 *Fair*	Prospective cohort Netherlands	Generation R Study women who were prenatally enrolled at gestational age >22 weeks, and had a singleton pregnancy between 2002-2006	▪ Socioeconomic status (neighbourhood-level deprivation based on housing, employment, education, integration, and safety)
Xiao 2014 *Fair*	Ecological China	Ethnically Han Chinese women from 3 hospitals of increasing socioeconomic and urban/rural status, and who did not have pre-existing hypertension, diabetes, or autoimmune diseases, whose pregnancies did not result from in vitro fertilization, between 2002-2011	▪ Socioeconomic status (neighbourhood-level, determined by socioeconomic and urban status of delivery hospital)
Social capital			
Azria 2016 *Fair*	Prospective multi-center cohort France	Singletons after 22 weeks of gestation in several urban centers, between 2010-2011. Outcomes were severe preeclampsia and eclampsia.	▪ Social capital (at least one of social isolation, insecure housing, unemployment, no insurance, undocumented migrant, and recent immigrant)

Bilano 2014 *Good*	Cross Sectional 23 developing countries in Africa, Latin America and Asia	All pregnant women admitted for delivery in the study's participating hospital centres in developing countries, between 2004-2005 (Africa and Latin America) and 2006-2007 (Asia)	▪ Social capital (operationalized as marital status)
Borovich 2018 *Poor*	Retrospective cohort Israel	Singleton deliveries of local and immigrant/asylum seekers delivered at one tertiary centre between 2012-2016	▪ Immigrant or asylum seeker vs. native resident
Cosson 2015 *Fair*	Retrospective cohort France	Women aged 18+ who were diagnosed with gestational diabetes mellitus, who spoke French and did not have a prior diagnosis of pregestational diabetes, between 2009-2012	▪ Social capital (EPICES French deprivation score evaluating individual's material goods, social networks, healthcare and leisure)
Demirci 2017 *Fair*	Cross-sectional Turkey	Hospital-based singleton live births. Cases were Syrian refugees; controls were Turkish women in the same hospital in 2015	▪ Refugee status
Lawlor 2005 *Good*	Retrospective cohort Ireland	Pregnancies complicated by preeclampsia compared to pregnancies not complicated by any hypertensive disease, between, 1969-1999	▪ Social capital during childhood (based on father's occupation), social capital during adulthood (based on husband's occupation)
Lisonkova 2013 *Good*	Retrospective cohort United States	Singleton deliveries in Washington State between 2003-2008. Outcome of interest was early or late-onset preeclampsia/eclampsia	▪ Marital status
Margioula-Siarkou 2013 *Fair*	Retrospective cohort Greece	Singleton pregnancies taking place in a tertiary hospital in Northern Greece, which has many immigrants from Albania and former Soviet Union, between 2003-2009	▪ Immigrant status
Nilsen 2018 *Good*	Retrospective cohort	Singleton pregnancies of ethnically Norwegian women (woman and both her parents	▪ Immigrant status

	Norway	born in Sweden), other Nordic women, and first-generation immigrant women (woman and both her parents are foreign-born), between 1990-2013	
Ortiz 2019 *Fair*	Cross Sectional Chile	All women of childbearing age in central Santiago hospital, in 2015	▪ Immigrant status
Schneider 2011 *Good*	Retrospective cohort Germany	All women who delivered in Germany in 2006 without diabetes mellitus	▪ Nationality by immigrant status (German, Eastern Europe, Mediterranean Neighbour, Other)
Sole 2018 *Good*	Retrospective cohort Norway	Singleton pregnancies without any major congenital abnormalities, between 1999-2014	▪ Immigrant status (maternal country of birth, by 11 different region categories)
Tessema 2015 *Good*	Cross Sectional Ethiopia	Hospital-based pregnant women who attended antenatal care, with gestational age greater than 20 weeks in 2013	▪ Marital status
Urquia 2014 *Good*	Cross country comparative retrospective cohort Australia, Canada, Denmark, Sweden, Spain, U.S.A	Women giving birth in participating centres across the included countries, who had country of origin data, between 1995-2010	▪ Immigrant status (according to maternal region of birth)

Table 2.2: Outcome and definition reported in the included studies.

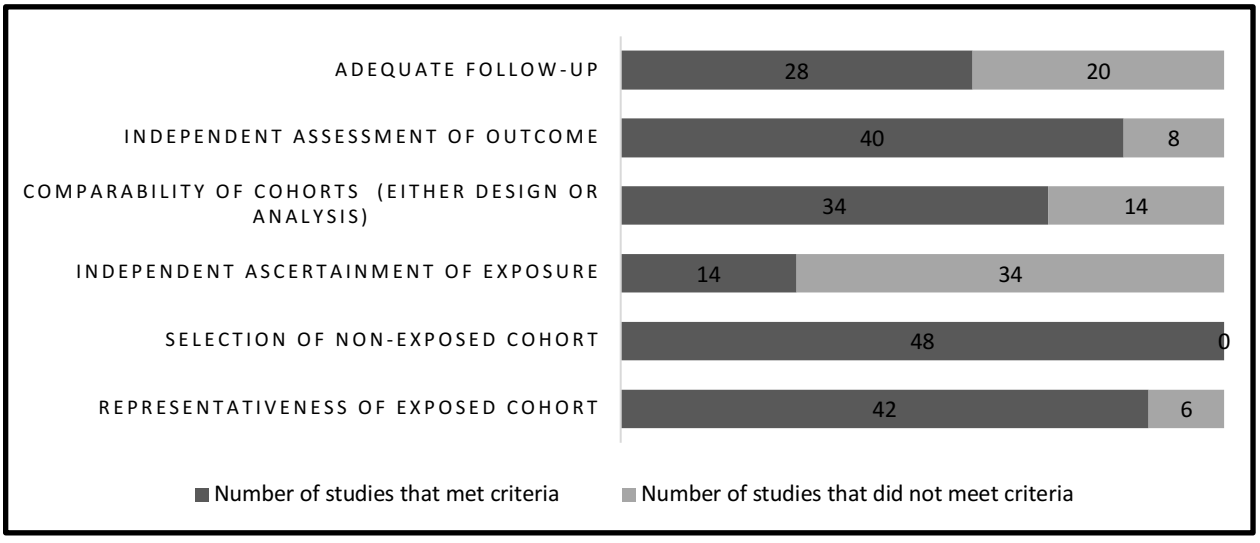
Outcome and definition	N	Studies' reference number
Hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg] after 20 weeks of gestation plus the presence of proteinuria	18	41,48-51,53-57,59,60,63,64,68,73,76,78
Hypertension (diastolic blood pressure ≥90 mmHg) and proteinuria	2	52,74

Gestational hypertension combined with proteinuria or other end-organ damage or HELLP syndrome	3	61,66,67
Eclampsia	3	28,76,78
Preeclampsia or eclampsia as a combined variable (ICD9 codes 642.4-642.6)	4	27,38,42,44
All severities of preeclampsia and eclampsia, including chronic hypertension superimposed by preeclampsia (ICD9 codes 642.4-642.7)	8	29-31,43,46,47,62,77
Preeclampsia reported based on gestational age. Early-onset (<34 weeks) and late-onset (≥ 34 weeks)	1	27
Preeclampsia or HELLP (ICD 10 codes O14.0, O14.1, O14.2, O14.9) additionally treated with $MgSO_4$	1	71
Preeclampsia definition not specified	15	19,32-37,39,40,45,58,65,69,70,75

2.3.2 Quality assessment of included studies

Two reviewers, SF and BM, reviewed and scored the methodological quality of the 52 included papers. Disagreements on individual criteria were resolved by discussion and consensus, and reasons for decisions were recorded. With 32 studies deemed "Good", 15 as "Fair" and five as "Poor" according to the pre-determined scoring criteria, the overall quality of the included papers was quite high. Figure 2.2 below shows the number of studies that met or did not meet specific criteria.

(A)



(B)

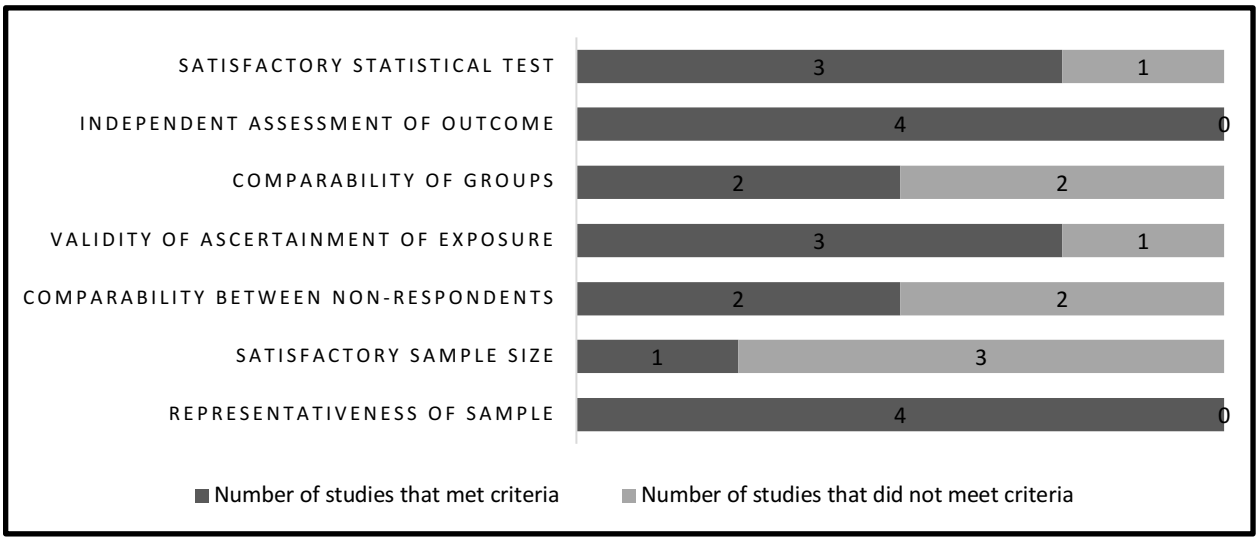


Figure 2.2: Quality assessment according to specific criteria in the modified Newcastle Ottawa Scale for cohort and ecological studies **(A)** and for cross sectional studies **(B)**.

The quality of the cohort and ecological studies is as follows: Six studies assessed populations that were not representative of the exposed cohort of interest, such as through choosing a select group,[33,75] a group of volunteers,[49,54,59] or not providing a description.[32] All the studies selected a non-exposed group from the same underlying cohort of the exposed. Thirty-four studies, the majority of which were ethnicity studies, ascertained the social determinants through self-report. Fourteen studies[19,27,32,33,49,52,56,59-61,63,65,68,75] did not ensure comparability of groups by either restricting the study population, stratifying results by potential confounders, or through adjusting for important confounders such as age, parity, and pre-existing conditions. Eight studies did not fill the criteria for assessment of outcome that was independent from exposure, by either not specifying if clinical outcome ascertainment was blinded and independent,[33,61] or by not providing sufficient information on the methodology.[32,37,58,63,65,75] Twenty studies did not provide a statement on loss-to-follow-up in the cohort, or did not provide a description of those lost to follow-up or those excluded from the main cohort due to missing information.[19,28,32-36,38-42,58,59,63,65,66,68,73,77]

The quality of the cross sectional studies is as follows: all studies chose samples that were representative of the exposed cohort of interest; three studies did not justify a satisfactory sample size;[69,70,76] two studies did not ensure comparability between respondents and non-respondents;[69,70] one study did not indicate how the exposure of interest was ascertained;[69] two studies did not

ensure comparability of exposed and unexposed through adjusting for important confounders;[69,70] all studies filled the criteria of assessing preeclampsia outcome independently of exposure; and one study did not describe a satisfactory statistical test.[69]

2.3.3 Relationships between SDOH and preeclampsia

2.3.3.1 Place of Residence

Only one study investigating the relationship between rural versus urban residence and preeclampsia was included in this review.[72] A Canadian cohort study, its study population included almost all deliveries occurring in British-Columbia, and sought to detect inequalities in severe adverse birth outcomes between women living in rural and urban geographic areas. The study reported finding no association between living in a rural area and preeclampsia (OR 0.98, 95% CI 0.87-1.11). Interestingly, however, women living in rural areas had 145% (aOR 2.45; 95% CI 1.59-3.77) increased odds of eclampsia compared to their urban counterparts, adjusting for pregnancy risk factors (e.g. age, prior comorbidities, parity, low socioeconomic status, etc.), as well as for labour and delivery risk factors (e.g. forceps use, labour induction, etc.).[72]

2.3.3.2 Race and ethnicity

Black Race

A total of 18 studies reported measures of relationships between Black race and preeclampsia. All but two, which were conducted in the U.K.[81] and in the Netherlands [52] were conducted in the U.S. Figure 2.3 displays the effect measures of all studies assessing Black race (including African-American race and Afro-Caribbean race). Although the magnitude of effect is different, the direction of relationship is the same, demonstrating higher odds of preeclampsia in Black compared to White populations. These cross-country disparities in preeclampsia between Blacks and Whites seems to support this association. Meta-analyses of all retrospective cohort studies, regardless of country, yielded a high I^2 value (I^2>90%), and subgroup analysis was conducted. A subgroup analysis among U.S. retrospective cohort studies[30,43,46] assessing similar definitions of preeclampsia (a combined variable of preeclampsia, eclampsia, and chronic hypertension superimposed on preeclampsia), in a general population (i.e. not restricted to high or low risk population) was attempted, but similarly yielded a result with high statistical heterogeneity (see Figure S1 in Appendix 6).

Next, to further explore heterogeneity in the U.S. studies, analyses of high-risk and low-risk groups were undertaken. Six retrospective cohort studies chose higher-risk populations, including women who were older,[19] teenaged,[36] diabetic,[31,35] obese,[34] or with chronic hypertension.[39] The disparity between African-American and White women, although still present, became statistically insignificant when pooling together the estimates from the higher-risk population studies (see Figure S2A in Appendix 6). Three U.S. studies chose low-risk populations for analysis, including women without diabetes or hypertension,[45] women without pre-existing chronic hypertension, diabetes, renal disease, or pregestational diabetes[44] and women without pre-existing hypertension.[38] The racial disparity was observed in the lower-risk populations, as well, with Black women experiencing 80% higher odds of preeclampsia (see Figure S2B in Appendix 6). The risk-based subgroup analyses are limited by the high unexplained heterogeneity and are thus not shown in the main results section.[23] A possible driver of this is the methodological heterogeneity across these studies, as the definitions of preeclampsia were variable and did not have sufficient similarity to allow for further subgroup analyses.

Quantifying the relationship between African-American race and preeclampsia in different states was undertaken in order to attempt to achieve a more homogeneous meta-analysis. Figure 2.11 shows subgroup analyses according to geographic location in the U.S (California, New York State, New York City, and southern states). With a heterogeneity of I^2=0%, studies taking place in New York City[31,46] yielded a pooled OR (pOR) of 1.67 (95% CI 1.64, 1.71), and studies taking place in southern U.S. states[29,43] yielded a pOR of 1.36 (95% CI 1.34, 1.39).

	Black		White		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	IV, Random, 95% CI	Year
Shen 2005	2634	161780	6296	643179	1.67 [1.60, 1.75]	2005
Caughey 2005	661	12639	2163	57660	1.42 [1.29, 1.55]	2005
Brown 2007	564	5555	182	2263	1.29 [1.08, 1.54]	2007
Tanaka 2007	14853	450098	25949	1297460	1.67 [1.64, 1.71]	2007
Nguyen 2012	140	1770	409	11139	2.25 [1.85, 2.75]	2012
Gong 2012	6386	138818	5284	264210	2.36 [2.28, 2.45]	2012
Fong 2013	164	121017	596	1057420	2.41 [2.02, 2.86]	2013
Zhang 2013	29517	420576	30630	584290	1.36 [1.34, 1.39]	2013
Penfield 2013	57	824	18	317	1.23 [0.71, 2.13]	2013
Sabol 2014	799	2991	1371	6378	1.33 [1.20, 1.47]	2014
Marshall 2014	859	9222	3949	41143	0.97 [0.90, 1.05]	2014
Ghosh 2014	1089	11584	1600	30499	1.87 [1.73, 2.03]	2014
James-Todd 2014	284	2181	116	1338	1.58 [1.26, 1.98]	2014
Booker 2018	14385	158075	83031	1566619	1.79 [1.76, 1.82]	2018
Ross 2019	5216	111801	16803	607151	1.72 [1.67, 1.77]	2019

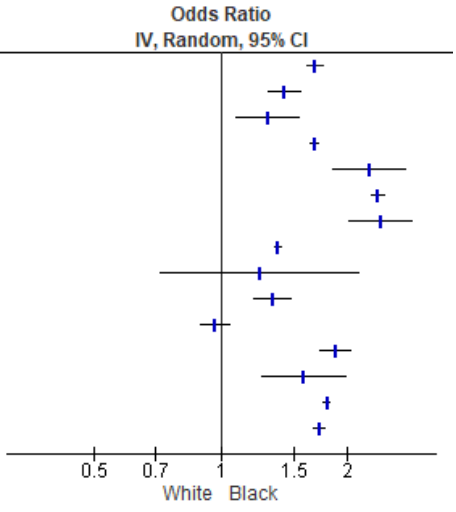


Figure 2.3: Forest plot of studies assessing effect estimates of Black vs. White race. Kernberg et al.[32] assessed each of the race/ethnicities in relation to preeclampsia but did not provide sufficient raw numbers and is thus discussed above. Fong et al. assessed the outcome of eclampsia, and not preeclampsia.[28]

Hispanic Ethnicity

Fourteen U.S.-based cohort studies evaluated Hispanic ethnicity compared to White race in relation to preeclampsia or eclampsia, as shown in Figure 2.4. The findings across these studies were inconsistent, with two demonstrating Hispanic ethnicity to be protective,[29,43] others showing Hispanic race to be a risk factor, [30,31,35,44,46], and still others suggesting no significant differences in preeclampsia between the two groups.[32] [28,39-41,45] Interestingly, out of the five studies showing higher occurrence of preeclampsia among Hispanics, one was set in New York City[44] and two were set in New York State.[31,44,46] The other two took place in California[35] and across the U.S.[30] The two studies showing Hispanic ethnicity to have an inverse relationship with preeclampsia both take place in southern states, among receivers of Medicaid insurance.[29,43]

To decipher the root of the highly variable findings, subgroup meta-analyses were undertaken. First, studies were grouped together according to high- versus low-risk populations of interest. The pooled estimates had very high heterogeneity (I^2>90%) and showed that Hispanic women in the high risk group[31,35,36,39] as well as in the low risk group[41,44,45] did not have statistically significant elevated odds of preeclampsia compared to White women (see Figure S4 in Appendix 6). Geographical area was then considered as the subgroup variable: meta-analyses of studies set in California,[35,39,45] and in New York State,[31,46] and southern U.S. states, were undertaken separately. The California studies, when pooled, showed high heterogeneity (see Figure S5 in Appendix 6); studies in New York State revealed a 1.52 times higher odds of preeclampsia in Hispanics compared to Whites (pOR=1.52, 95% CI 1.48-1.55, I^2=0%); and studies in southern States showed a 15% reduced odds in Hispanics compared to Whites (pOR= 0.85, 95% CI 0.75-0.97, I^2=51%). The latter two meta-analyses are displayed in Figure 2.11. The variability in effect estimates across the studies could also be partially explained by a change in trends over time. Tanaka et al. stratified rates of preeclampsia in New York City according to the year of delivery, and found that the disparity between Hispanics and Whites narrowed by the year 2002.[46]

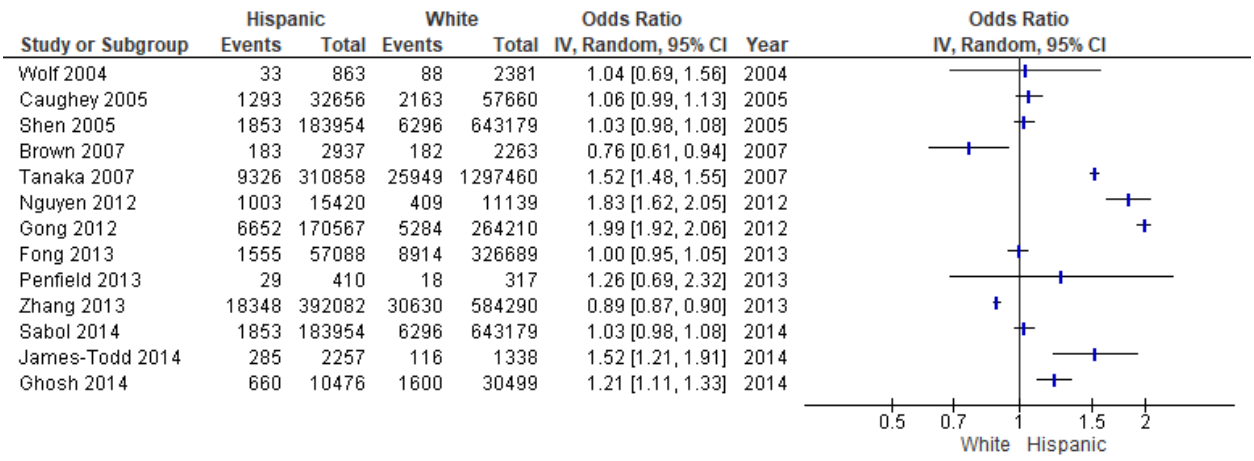


Figure 2.4: Forest plot of studies assessing effect estimates of Hispanic ethnicity vs. White race. Kernberg et al.[32] assessed race/ethnicities in relation to preeclampsia but did not provide sufficient raw numbers and is thus discussed above. Fong 2013[28] assessed the outcome of eclampsia, and not preeclampsia.

Asian Race

Among the 14 studies that included any Asian race in their analyses, one was set in New Zealand,[67] and one in the U.K.,[57] while all the others were U.S.-based. The definition of 'Asian' was different across studies, with six studies including simply an 'Asian' category in their analyses;[36,39,40,45,52] two studies differentiating between 'East Asian' and 'South Asian' categories;[31,57] two studies including an Asian/Pacific-Islander group;[28,30] and four studies assessing specific Asian groups such as Chinese, Japanese, and Filipino.[37,44,47,67] Asian race represents a myriad of different racial/ethnic groups, and grouping these together appeared to lead to inconsistent results. Figure 2.5 shows a forest plot of studies using the 'Asian' categorization, with effect estimates spread widely. A pooled estimate was not attempted due to the highly diverse definitions of Asian ethnicity across the studies.

Studies which had chosen instead to categorize ethnicities more specifically by country of origin found that Filipino ethnicity conferred an augmented risk, and that Chinese ethnicity was associated with a protective effect for preeclampsia, compared with White women.[44,47] Further, a Hawaii study[47] reported that although Chinese and Filipino women had significantly different preeclampsia rates compared to Whites (2.0%, 4.6%, and 2.9%, respectively), this relationship may have been modified by age, multiple gestation, and obesity. More specifically, Chinese women indeed had significantly lowered risk of preeclampsia among younger, non-obese women giving birth to singletons (OR 0.64, 95% CI 0.53-0.78). But among all other high risk

stratifications, this protective effect disappeared.[47] Similarly, Filipino women had increased odds compared to Whites (OR 1.55, 95% CI 1.43-1.67), but once obesity was taken into account this association disappeared.[47] Anderson et al. found in a New Zealand cohort that Chinese women had significantly reduced odds of preeclampsia compared to women of European ethnicity, adjusting for body mass index, age, parity, smoking, socioeconomic status, and comorbidities.[67]

Rao et al.[37] looked at preeclampsia among Japanese, Chinese, and Filipino women, and found their risk of disease to be 3.7%, 4.0%, and 6.8%, respectively. After adjusting for multiple confounding variables, Chinese women did not have significantly different odds of preeclampsia compared to Japanese women. The study did not include White women, making the comparison to other studies difficult.[37] Despite this, this study showed that these Asian subgroups do not have similar incidence of disease, which may explain the high variability in outcomes of studies that simply had an 'Asian' race group.

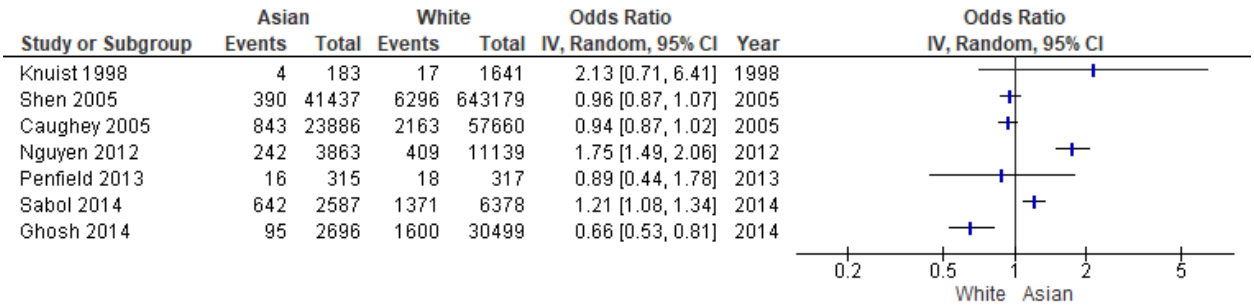


Figure 2.5: Forest plot of studies assessing effect estimates of Asian vs. White race. Kernberg et al.[32] assessed race/ethnicities in relation to preeclampsia but did not provide sufficient raw numbers and is thus discussed above. Fong 2013[28] assessed the outcome of eclampsia, and not preeclampsia.

Native/Indigenous Race

Six studies assessed any Indigenous/Native race and preeclampsia outcome. In the U.S., three studies investigated 'Native-American',[28,32,45] one study investigated 'Hawaiian Native,'[47] and one assessed 'American-Indian/Alaska Native'[42] race in comparison to Whites. A study set in New Zealand assessed Maori compared to European race.[67] People belonging to their country's Native race had higher odds of preeclampsia, as can be seen in Figure 2.6. Kernberg et al. reported no differences between Native-American and Caucasian.[32] The study by Fong et al. reported that eclampsia odds was not different between the two groups.[28] As displayed in Figure 2.11, a meta-

analysis of the two U.S. studies[42,45] (excluding Hawaii natives)[47] showed that Native American women had an 11% increased odds of preeclampsia compared to White women (pOR 1.11, 95% CI 1.02-1.21, I^2=0%).

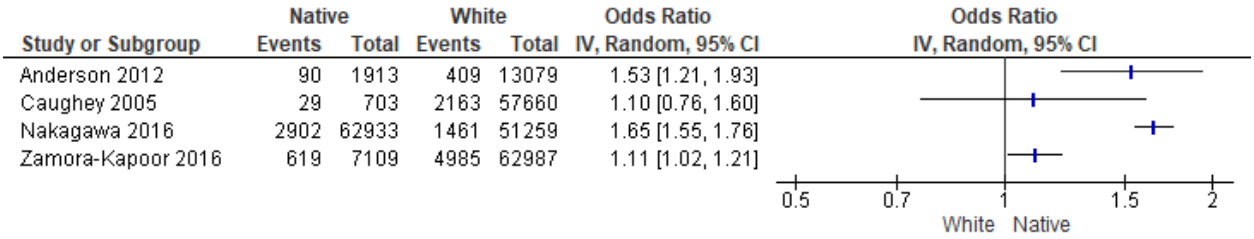


Figure 2.6: Forest plot of studies assessing effect estimates of Native vs. White race. Kernberg et al.[32] assessed race/ethnicities in relation to preeclampsia but did not provide sufficient raw numbers and is thus discussed above.

2.3.3.3 Occupational/employment status

The role of maternal employment status in preeclampsia was assessed in three retrospective cohort studies[51,66,75] and one prospective cohort study[33] in this systematic review. The studies defined employment differently, with the German study creating different categories of occupation according to skill level,[66] the Generation R Netherlands study providing subcategories of unemployment as 'housewife,' 'job-seeking,' 'receiving disability,' and student,'[51] the U.S. study on military wives dichotomizing the variable by 'work' and 'no work,'[33] and the Saudi-Arabia study of highly educated women using a dichotomy of 'employed' versus 'housewife'.[75] Due to the differing country setting, year of study, populations of interest, and operationalization of employment variable, pooling the effect estimates was deemed inappropriate, and individual results will hence be reported here, and visualized in Figure 2.7. Three of the studies found no statistically significant differences between women who were employed and unemployed.[33,51,75] This was true for all the unemployment subgroups in the study by Jansen et al.[51] In the German perinatal cohort study, women who were housewives had significantly lower odds of preeclampsia compared to women who worked in higher service management. The difference disappeared after adjusting for all other variables in the model (age, nationality, body mass index, multiple births, and diabetes, among others).[66] In this study's analysis, unskilled workers and middle service workers, however, had higher odds of preeclampsia compared to high skilled workers, and this disparity persisted after adjusting for all other variables in the model.[66]

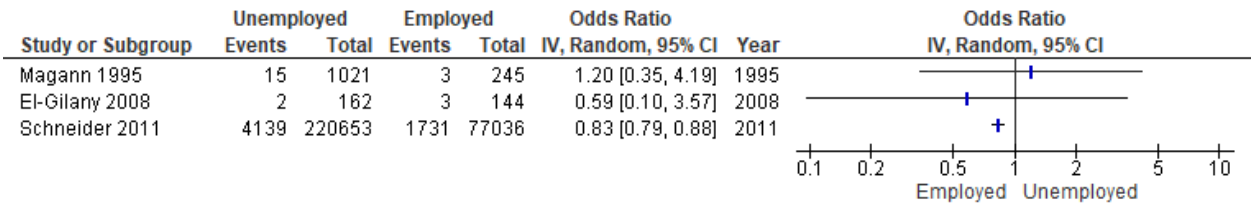


Figure 2.7: Forest plot of studies assessing the association between employment status and preeclampsia. Jansen 2010[51] did not provide raw totals and its results are discussed above.

2.3.3.4 Education

The role of maternal education on the outcome of preeclampsia was assessed by seven studies. Four were retrospective cohort studies,[27,31,55,62] one was a prospective cohort study,[48] and two were cross sectional studies.[64,76] Education was used as a proxy for maternal socioeconomic status in some of these studies.[48,62]

A pooled analysis of the retrospective cohort studies gave a pOR with high heterogeneity (see S6). Overall, three of the cohort studies, which were conducted in the U.S.,[27,31] and Sweden,[62] did not find a significant difference in preeclampsia between women with low and high educational attainment. An inverse gradient effect was found in the Netherlands,[48] and Norway,[55] with preeclampsia odds increasing with decreasing maternal education. Results of the former study are limited by the wide confidence intervals.[48] More evident effects were found within the cross-sectional studies, which both took place in low-resource settings. Bilano et al.[76] analyzed data from 23 developing countries in Africa, Asia, and Latin America, and Tessema et al.[64] looked at preeclampsia prevalence in Ethiopia. A meta-analysis of these two studies (Figure 2.11) showed that women with lower education had 149% higher odds of preeclampsia compared to those with higher levels of education (pOR 2.49, 95% CI 1.94, 3.20, I=0%). The cross-country study had a much higher sample size and thus was driving this pOR. Upon a closer inspection of the results of this study, it was found that although women with no education had 22% (aOR 1.22, 95% CI 1.07-1.39) higher odds of preeclampsia compared to highly educated women (post-secondary/tertiary education), women with some education (lower or upper secondary education) did not have significantly different odds compared to the same highly educated women, after adjusting for age, body mass index, parity, comorbidities, country, institution, and other variables.[76] These results demonstrate that in this cross-sectional study of low-resource countries, women with some secondary education were lifted out of the worst disparities of preeclampsia, and experienced similar occurrence of the disease as the very highly educated.[76]

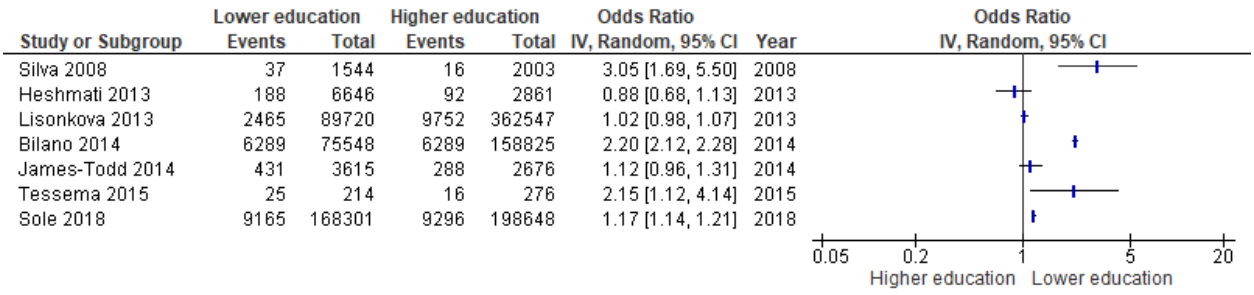


Figure 2.8: Forest plot of studies assessing the association between educational attainment and preeclampsia. Education was dichotomized into "Lower" and "Higher" for each study by grouping together the lowest and highest attainment groups, respectively. Bilano 2014[76] data was grouped as "lower": none, primary, and lower secondary and "higher": upper secondary, and post-secondary/tertiary. Sole 2018[55] was grouped as "lower": none/primary or secondary school and "higher": Bachelor/Masters/PhD"; Silva 2008[48] data was grouped as "lower": no education, primary school, lower vocational training, intermediate general school or 3 years or less general secondary school) and mid-low (than 3 years general secondary school, intermediate vocational training or first year of higher vocational training) and "higher": mid-high (higher vocational training) and high education (university or PhD degree). Heshmati 2013[62] data was grouped as "lower": compulsory schooling and upper secondary schooling and "lower": any postsecondary schooling. Lisonkova 2013[27] data was grouped as "lower": less than high school and "higher": high school or more. James-Todd 2014[31] data was grouped as "lower": 12 years or less and "higher": more than 12 years of schooling.

2.3.3.5 Socioeconomic status

Eight primary studies evaluated the relationship between neighbourhood-level socioeconomic status and the occurrence of preeclampsia. All studies were from different countries, namely China,[68] Norway,[54] Netherlands,[49] New Zealand,[67] Sweden,[63] Korea,[71] Spain,[73] and the U.S.[46] All studies assessed socioeconomic status as ecologic variables of interest, meaning the variables were based on geographical or neighbourhood measures, and not personal characteristics. One study took an entirely ecological approach to the study, where the outcome of interest was area-based prevalence of preeclampsia, which was compared across hospitals of differing levels of urbanity and wealth.[68] Neighbourhood-level socioeconomic status was defined in different ways, such as neighbourhood-level income quintiles,[67] household-level income inequality,[71] urbanity and wealth of the geographical area of living,[82] and of hospital of delivery,[68] township-based immigrant population percentage, median income, and percentage of population on welfare,[63] the Human Development Index of the maternal country of origin,[73] percentage of

residents living under the poverty line,[46] and 'neighbourhood deprivation', a measure which integrates factors such as an area's housing, employment, education, integration, and safety.[49]

Figure 2.9 shows that socioeconomic status was associated with higher odds of preeclampsia in all the included studies, except for the household income level study by Choe et al.[71] This outlier might be driven by the fact that this study restricted their preeclampsia definition to only very severe forms treated by $MgSO_4$. Although different in setting, three retrospective studies were deemed similar enough in terms of exposure of interest because of the focus on neighbourhood-level measures of inequality, and their effect measures were pooled together.[46,63,67] Women living in more deprived neighbourhoods had 46% (pOR 1.43; 95% CI 1.33-1.54; I^2 =15%) increased odds of preeclampsia, compared to women living in less deprived areas (Figure 2.11).

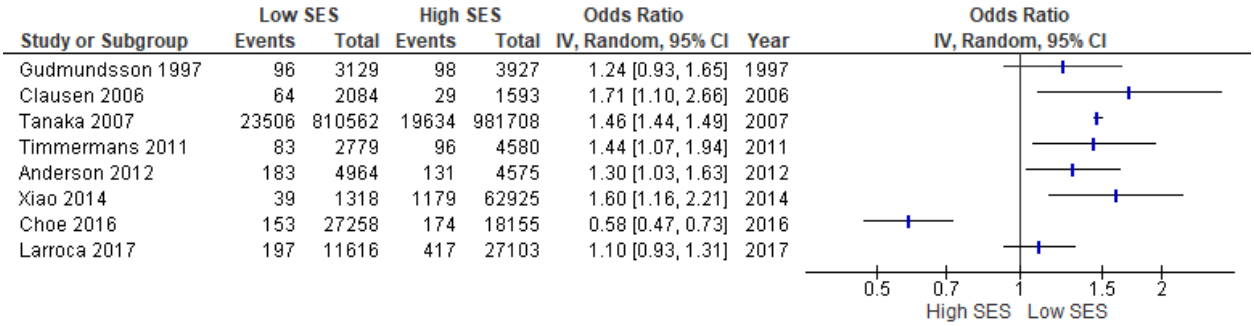


Figure 2.9: Forest plot of studies assessing the association between socioeconomic status and preeclampsia. Choe 2016[71] evaluated neighbourhood-level and severe preeclampsia treated with $MgSO_4$. The plot displays odds ratios of studies looking at ecologic neighbourhood-level measures, as well individually-ascribed measures (see Table 2.1 for details on specific studies). Socioeconomic status was dichotomized into "Lower" and "Higher" for each study by grouping together the lowest and highest quantile groups, respectively.

2.3.3.6 Social capital

Marital status

Three studies assessed a woman's marital status at the time of delivery and her odds of preeclampsia: one cross-country large scale cross-sectional study,[76] one hospital-based cross-sectional study set in Ethiopia,[64] and a U.S. based retrospective cohort study.[27] All three studies found that married women had statistically significant lower odds of preeclampsia compared to unmarried women (see Figure 2.10A). A pooled analysis of the two cross-sectional studies yielded an estimate associated with a high heterogeneity value (see Figure S7 in Appendix 6).

Immigrant/refugee status and religion

In the context of SDOH, immigrant status and religion will be discussed together here in terms of the preeclampsia disease incidence of minority populations. There was one retrospective cohort study from Greece that evaluated religion. More specifically, the study assessed the difference in preeclampsia rates between the majority Christian Orthodox and minority Muslim women, and found that the latter group had an almost two-fold rate of preeclampsia or eclampsia, although small cell sizes limit this finding.[61] Eight studies, including two cross sectionals,[69,70] five retrospective cohorts,[53,55,60,65,66] and one cross-country comparative retrospective cohort study,[77] looked at the immigrant status of women and its relation to preeclampsia. Immigrant status was considered an indicator of social capital, as it affects how a woman might access resources through her social positioning as an immigrant. Studies analysed the difference in preeclampsia rates between natives versus immigrant groups, although a few studies operationalized immigrant status not according to immigrant status, but according to country of origin.[55,66,77] It is thus difficult to make conclusions on immigration in general, and not on the possible effect of immigrating from specific countries, or of separating race from the effect of immigration.

As can be seen in Figure 2.10B, immigration conferred a protective effect against preeclampsia in five of the studies, and conferred an augmented risk for the two studies assessing preeclampsia in refugees[69] and in asylum seekers/migrant workers.[65] Urquia et al.'s[77] cross-country study on immigration in industrial countries found a significantly higher odds of preeclampsia as well as eclampsia among immigrant women from Sub-Saharan Africa, and from Latin America and the Caribbean, compared to immigrant women from Western Europe, as well as compared to the non-immigrant populations. Women from other regions had lower odds of disease in comparison to the receiving country women. Patterns of disparities between immigrants from specific regions were different across the countries under study, with Spain exhibiting the broadest disparities, and Australia having the narrowest disparities.[77]

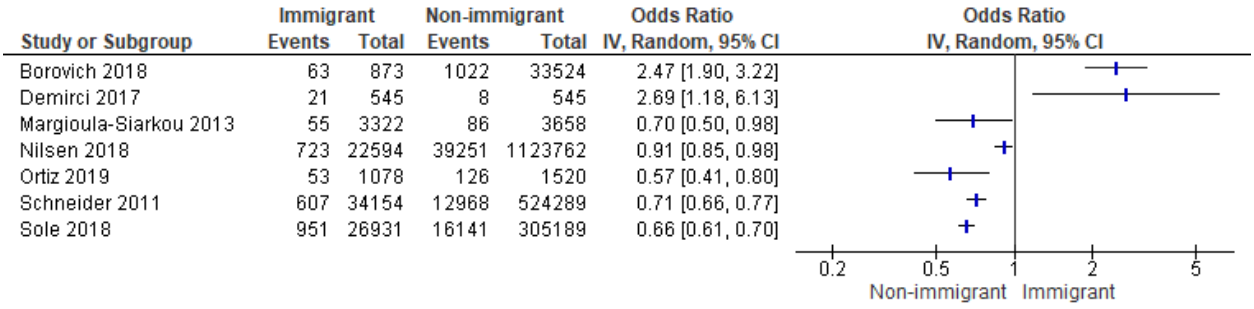
Interestingly, in an attempt to separate the effects of the social experience of immigration from that of ethnicity or of country of origin, two European studies categorized immigrants from neighbouring European countries in a separate group.[55,66] These two studies, set in Norway and Germany, found that immigrants from neighbouring, socioeconomically-similar countries, had lower odds of preeclampsia compared to Norwegian or German native-born women, respectively.

In Norway, neighbouring immigrants had 29% reduced odds of preeclampsia,[55] while in Germany, neighbouring immigrants had a 15% reduced odds, compared to non-immigrant women.[66]

Other social capital associations

Studies that focused on social capital, isolation, networks, and family or community support systems, other than marital status or immigrant status, were clustered here for analysis. Three studies examined social connectivity factors that could give rise to advantages or disadvantages in maternal health outcome; two cohort studies from France[58,59] and one from Ireland.[74] Given that social capital can be operationalized in very different ways, a description of the indicators used in each study is as follows: Lawlor et al.[74] defined social class as husband's occupation (manual vs. non-manual); Cosson et al.[59] utilized a French deprivation score evaluating individual material goods, money, friendship and family networks, as well as healthcare and leisure; and Azria et al.[58] defined maternal social deprivation as at least one of social isolation, insecure housing, unemployment, no insurance, undocumented migrant, and recent immigrant. None of the studies had found a significant different between preeclampsia rates of women with low versus high social capital.

(A)



(B)

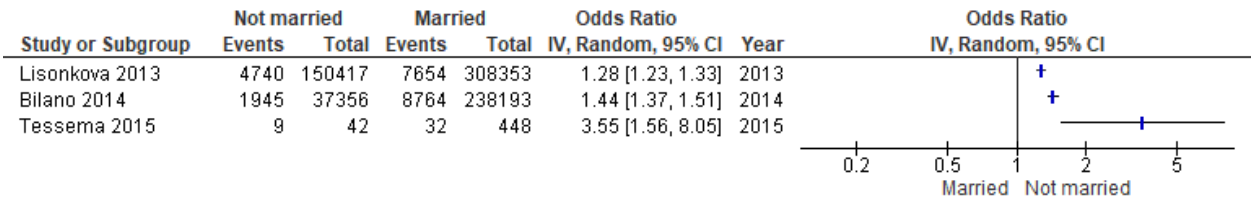
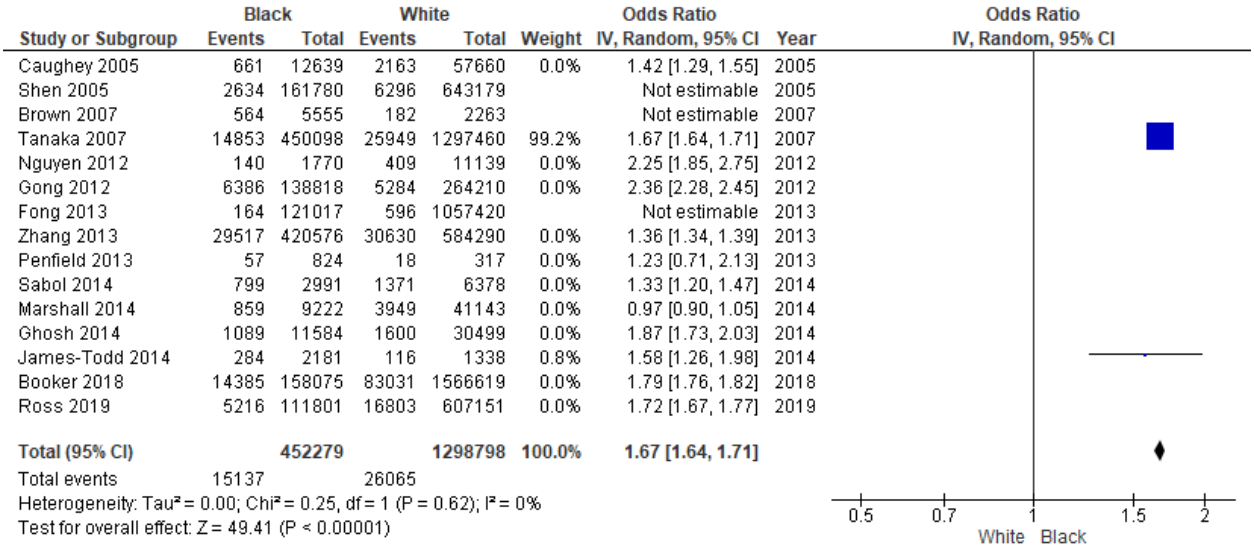
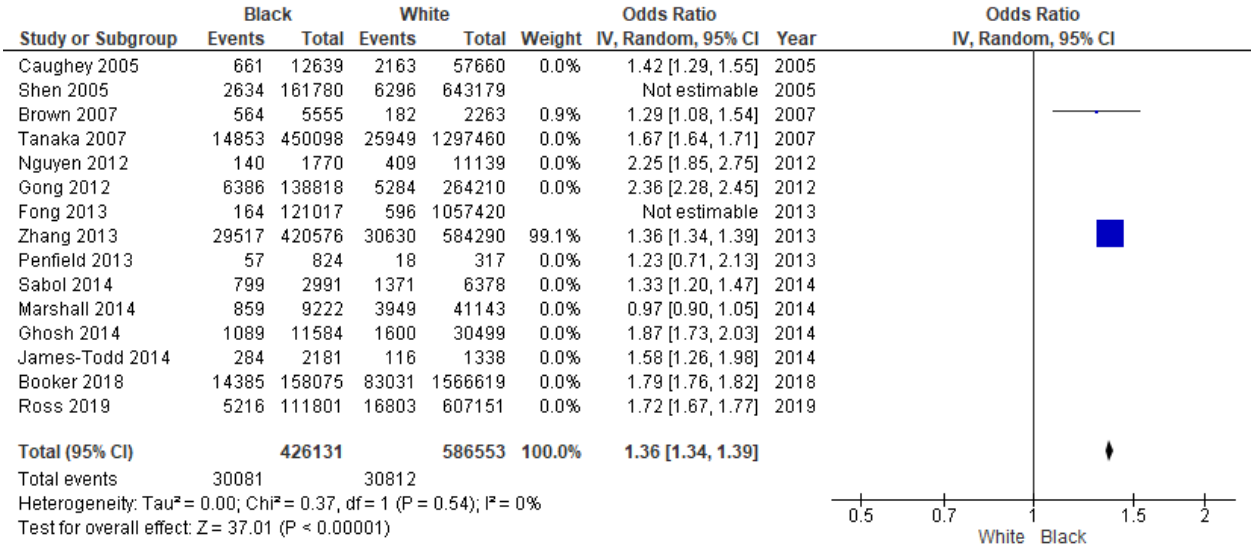


Figure 2.10: Forest plots of studies assessing the association between social capital and preeclampsia. Effect estimates of immigrant/refugee status **(A)**, and marital status **(B)**. Lawlor 2005,[74] Cosson 2015,[59] and Azria 2016[58] reported different social capital measures, and Urquia 2012,[83] although did assess immigrant status and preeclampsia, did not report raw numbers. These are discussed in the narrative analysis in the results section above.

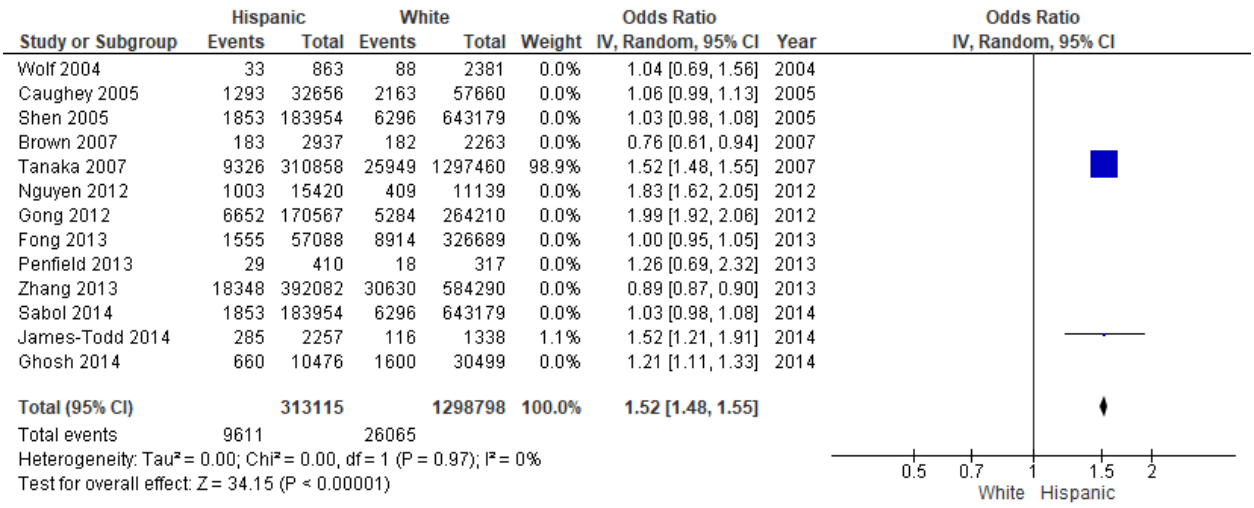
(A)



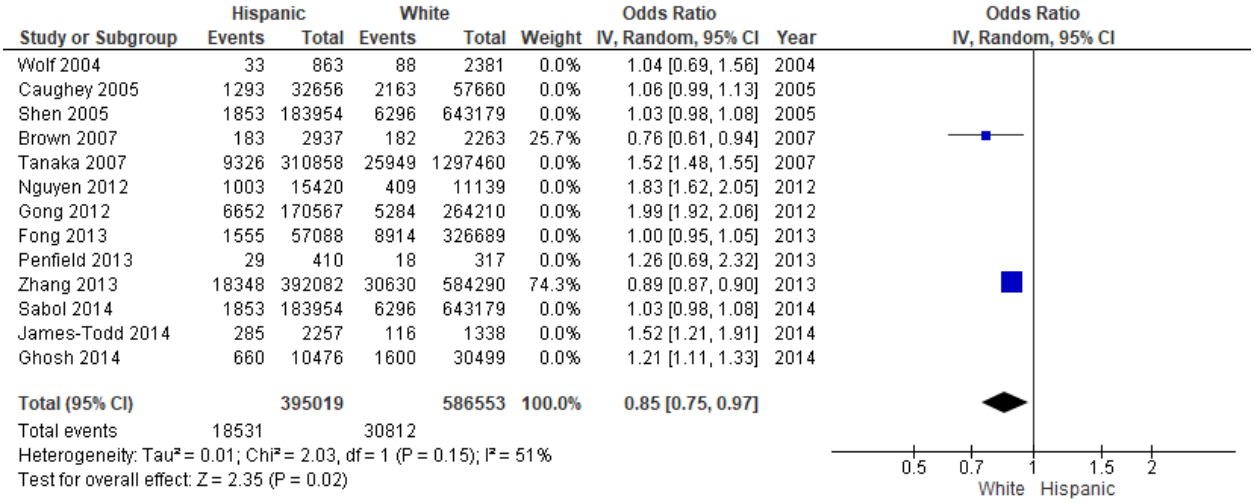
(B)



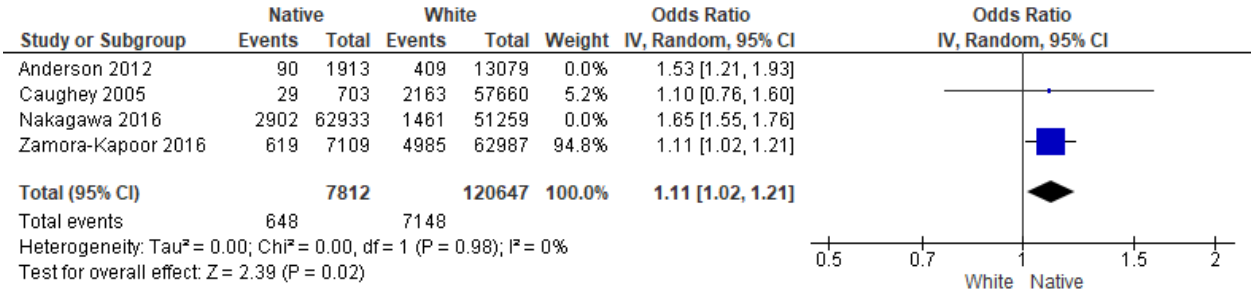
(C)


Hispanic
White
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Wolf 2004 33 863 88 2381 0.0% 1.04 [0.69, 1.56] 2004
Caughey 2005 1293 32656 2163 57660 0.0% 1.06 [0.99, 1.13] 2005
Shen 2005 1853 183954 6296 643179 0.0% 1.03 [0.98, 1.08] 2005
Brown 2007 183 2937 182 2263 0.0% 0.76 [0.61, 0.94] 2007
Tanaka 2007 9326 310858 25949 1297460 98.9% 1.52 [1.48, 1.55] 2007
Nguyen 2012 1003 15420 409 11139 0.0% 1.83 [1.62, 2.05] 2012
Gong 2012 6652 170567 5284 264210 0.0% 1.99 [1.92, 2.06] 2012
Fong 2013 1555 57088 8914 326689 0.0% 1.00 [0.95, 1.05] 2013
Penfield 2013 29 410 18 317 0.0% 1.26 [0.69, 2.32] 2013
Zhang 2013 18348 392082 30630 584290 0.0% 0.89 [0.87, 0.90] 2013
Sabol 2014 1853 183954 6296 643179 0.0% 1.03 [0.98, 1.08] 2014
James-Todd 2014 285 2257 116 1338 1.1% 1.52 [1.21, 1.91] 2014
Ghosh 2014 660 10476 1600 30499 0.0% 1.21 [1.11, 1.33] 2014
Total (95% CI) 313115 1298798 100.0% 1.52 [1.48, 1.55]
Total events 9611 26065
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 34.15 (P < 0.00001)
0.5 0.7 1 1.5 2
White Hispanic

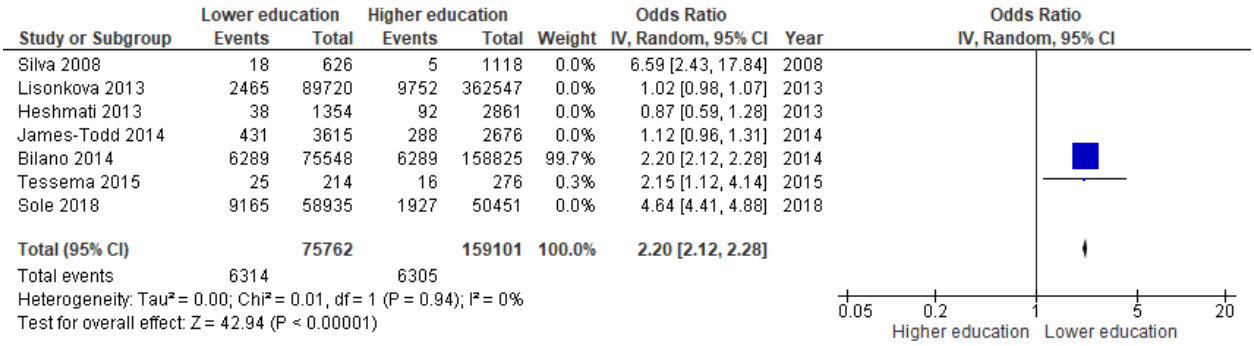
(D)


Hispanic
White
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Wolf 2004 33 863 88 2381 0.0% 1.04 [0.69, 1.56] 2004
Caughey 2005 1293 32656 2163 57660 0.0% 1.06 [0.99, 1.13] 2005
Shen 2005 1853 183954 6296 643179 0.0% 1.03 [0.98, 1.08] 2005
Brown 2007 183 2937 182 2263 25.7% 0.76 [0.61, 0.94] 2007
Tanaka 2007 9326 310858 25949 1297460 0.0% 1.52 [1.48, 1.55] 2007
Nguyen 2012 1003 15420 409 11139 0.0% 1.83 [1.62, 2.05] 2012
Gong 2012 6652 170567 5284 264210 0.0% 1.99 [1.92, 2.06] 2012
Fong 2013 1555 57088 8914 326689 0.0% 1.00 [0.95, 1.05] 2013
Penfield 2013 29 410 18 317 0.0% 1.26 [0.69, 2.32] 2013
Zhang 2013 18348 392082 30630 584290 74.3% 0.89 [0.87, 0.90] 2013
Sabol 2014 1853 183954 6296 643179 0.0% 1.03 [0.98, 1.08] 2014
James-Todd 2014 285 2257 116 1338 0.0% 1.52 [1.21, 1.91] 2014
Ghosh 2014 660 10476 1600 30499 0.0% 1.21 [1.11, 1.33] 2014
Total (95% CI) 395019 586553 100.0% 0.85 [0.75, 0.97]
Total events 18531 30812
Heterogeneity: Tau² = 0.01; Chi² = 2.03, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 2.35 (P = 0.02)
0.5 0.7 1 1.5 2
White Hispanic

(E)


Native
White
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Anderson 2012 90 1913 409 13079 0.0% 1.53 [1.21, 1.93]
Caughey 2005 29 703 2163 57660 5.2% 1.10 [0.76, 1.60]
Nakagawa 2016 2902 62933 1461 51259 0.0% 1.65 [1.55, 1.76]
Zamora-Kapoor 2016 619 7109 4985 62987 94.8% 1.11 [1.02, 1.21]
Total (95% CI) 7812 120647 100.0% 1.11 [1.02, 1.21]
Total events 648 7148
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 2.39 (P = 0.02)
0.5 0.7 1 1.5 2
White Native

(F)



(G)

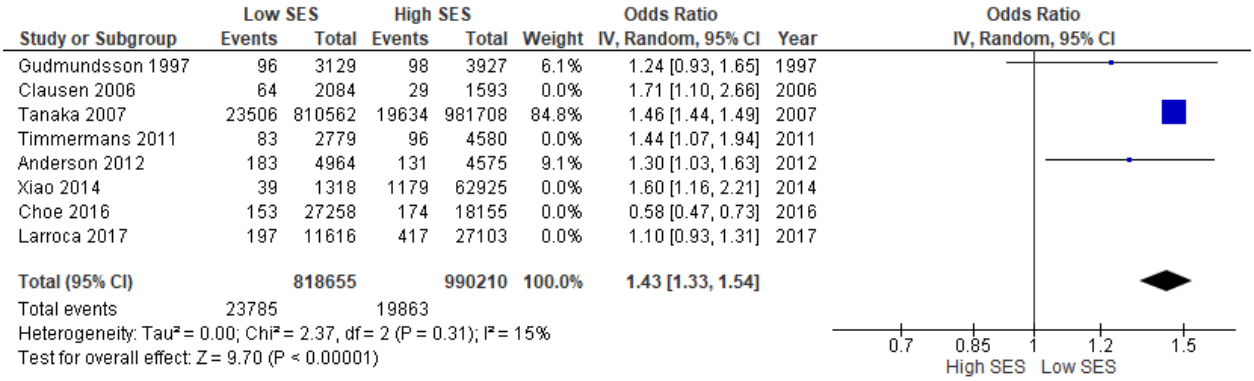


Figure 2.11: Meta-analyses of sufficiently homogeneous studies. **(A)** African-American race, retrospective cohorts, New York City only. **(B)** African-American race, retrospective cohorts, southern states only**. (C)** Hispanic ethnicity, retrospective cohorts, New York State only**. (D)** Hispanic ethnicity, retrospective cohorts, Southern States**. (E)** Native American in America, excluding Hawaii natives, retrospective cohorts. **(F)** Education, cross sectionals, developing countries**. (G)** Socioeconomic status, retrospective cohorts, ecological measures.

Table 2.3: Summary of findings of SDOH and preeclampsia occurrence. Pooled estimates are shown when possible, and adjusted single point estimates of studies with the highest quality score are displayed.

Social determinant of health	Subgroup	Sample size (number of studies) and study	Point estimate (95% confidence interval)
Rural vs. urban residence	Retrospective cohort in British Columbia, Canada	256,220 (1) Lisonkova 2016	aOR 0.98 (0.87-1.11)
African-American vs. White race	Retrospective cohorts, New York City	1,751,077 (2) James-Todd 2014, Tanaka 2007	pOR 1.61 (1.64, 1.71)*

	Retrospective cohorts, southern states only	1,012,684 (2) Brown 2007, Zhang 2013	pOR 1.36 (1.34, 1.39)*
Hispanic ethnicity vs. White race	Retrospective cohorts, New York State only	1,611,913 (2) Tanaka 2007, James-Todd 2014	pOR 1.52 (1.48, 1.55)*
	Retrospective cohorts, Southern States	981,572 (2) Brown 2007, Zhang, 2013	pOR 0.85 (0.75, 0.97)*
Native-American vs. White Race	Retrospective cohorts set in the U.S., excluding Hawaii	128,459 (2) Caughey 2005, Zamora-Kapoor,2016	pOR 1.1 (1.02, 1.21)*
Unemployed vs. Employed	Retrospective cohort Generation R Study women (city of Rotterdam study	5,994 (1) Jansen 2010	aOR 0.96 (0.60-1.53)
Lower education vs. Higher education	Cross sectionals, developing countries	234,863 (2) Bilano 2014, Tessema 2015	pOR 2.20 (2.12, 2.28)*
Socioeconomic status (low vs. high)	Retrospective cohorts, ecological neighbourhood level measures	1,808,865 (3) Gudmundsson 1997, Tanaka 2007, Anderson 2012	pOR 1.43 (1.33, 1.54)*
Social capital (immigrant vs. non-immigrant)	Retrospective cohort, nulliparous deliveries. Norway non-immigrants vs. Immigrants from other European countries.	332,120 (1) Sole 2018	aOR 0.71 (0.66-0.77)*
Social capital (unmarried vs. married)	Cross Sectional of 23 developing countries in Africa, Latin America and Asia	276,388 (1) Bilano 2014	aOR 0.98 (0.90–1.06)
	Retrospective cohort in Washington, U.S. (late-onset preeclampsia)	456,668 (1) Lisonkova 2013	aOR 1.14 (1.10-1.19)*

* signifies statistical significance

2.4 Discussion

Key Findings

This systematic review is the first to comprehensively evaluate the relationship between the SDOH and preeclampsia. A total of 52 epidemiological studies analysing preeclampsia or eclampsia occurrence stratified by one of the SDOH described by the PROGRESS-Plus framework were included. Moreover, this review features meta-analyses of the relationships between preeclampsia and Black race, Hispanic ethnicity, Native American ethnicity, education, and socioeconomic status. The biggest challenge in this review was the operationalization and definition of the SDOH, as well as highly variable population selection of each study. Despite the heterogeneity, our results suggest that some factors of social and material deprivation are positively associated with preeclampsia.

In particular, there was clear evidence that African-American race, Native-American ethnicity, lower socioeconomic status, and unmarried status, conferred higher odds of preeclampsia. Women of Hispanic ethnicity had more variable findings which seemed to depend on the location where the study took place, and not on the risk set of the population under study. Ethnicity studies assessing specific Asian groups found that prevalence of preeclampsia was highly variable within these ethnic groups, with Chinese women having lower, and Filipino women having higher, odds of preeclampsia compared to White women. Employment and occupational status did not demonstrate a clear relationship with preeclampsia, and the studies were limited by small sample sizes. The modest number of studies assessing the link between employment and preeclampsia also point to a paucity of evidence, especially in western countries. The inverse relationship between preeclampsia and educational attainment was particularly evident in lower-income countries, and was inconsistent in other settings. Social capital showed mixed results, depending on its operationalization. It was found that immigrants had lower occurrence of preeclampsia compared to non-immigrant women, except for refugees or asylum seekers and migrant workers, where the opposite pattern was demonstrated. Marital status was generally found to be protective, although few studies assessed this relationship.

Interpretation

In the included ethnicity studies, Black women were found to be at higher risk of preeclampsia compared to White women, regardless of country where the study took place, with the exception of the study on women with obesity[34] which will be discussed below. This cross-country disparity between the races may be dictated by upstream, structural disparities in SDOH

such as racism and discrimination. Interpersonal racism has been linked to physiological phenomena and pathophysiology of disease, such as inflammatory markers, allostatic load, and dysregulation of hormones.[84,85] Chronic or acute exposure to racism goes "beyond skin deep," as expressed by Berger and Sarnyai,[86] who presented evidence on mediating factors between discrimination and adverse mental health outcomes. They suggest that discrimination resembles chronic social stress, with higher cortisol levels, and over-activation of the hypothalamic pituitary adrenal (HPA) axis, which can lead to a maladaptive release of glucocorticoids and pro-inflammatory cytokines, and may lead to adverse metabolic changes.[86] The relationship between structural racism and adverse health outcomes was also found in CVD research, with Black people living in more racist states having higher odds of myocardial infarction than Blacks living in states considered as having low structural racism.[87]

This review attempted to elucidate further if a similar elevated risk existed in high-risk populations as well as lower-risk populations (i.e. women free of such clinical risk factors). Interestingly, in higher-risk populations (i.e. women with pre-existing diabetes, hypertension, obesity), African-American women did not consistently experience significantly greater odds of preeclampsia compared to Whites, suggesting that perhaps the observation can be explained by disproportionately higher burden of risk factors among African-Americans. Obesity, for example, is a known risk factor of preeclampsia,[88,89] and although obesity is more prevalent among African-American women,[90] it appears that their preeclampsia rates do not consistently differ from their obese White counterparts.[34,91] The same cannot be said among low-risk populations, however, where African-American women carry a higher burden of preeclampsia, similarly to general populations. Perhaps healthier states (e.g. no diabetes or hypertension) do not lend favourable outcomes equitably in pregnancy between the races.

As they pertain to Asian ethnicity, U.S. studies were deemed too heterogeneous due to the questionable amalgamation of different Asian ethnic groups. Similarly, the dichotomization of East and West Asian seems to not have been granular enough, and did not detect any significant differences in preeclampsia.[31,57] The conflicting studies seem to suggest that grouping all Asian ethnicities together, or even categorization by West and East Asian ethnicities, thus may lead to inaccurate estimates. A recent Canadian study has shown that obesity rates for Filipino women, for example, was 5% compared to 2% of other 'East Asian' women.[92] Considering the different

risk sets associated with different nationalities, future studies should correct for this by incorporating as much information about the specific origin of the woman as possible.

The finding that Chinese women had lower odds of preeclampsia in the two studies assessing Chinese ethnicity compared to White[47,67] is interesting, seeing as how prior studies did not distinguish this ethnicity from the general 'Asian' ethnic category. It is possible, however, that this finding could be explained by lower prevalence of risk factors such as obesity among Chinese compared to Whites. Indeed, in a U.S. maternal obesity study, Chinese mothers were the only ethnic group to have obesity rates decreased (by about 40%) over time.[90] It is possible, then, that the lower rates of preeclampsia among Chinese women could be explained by lower obesity rates, among other factors. This is corroborated by Nakagawa and colleagues' finding that once obesity, age, and parity is taken into account, difference in odds of preeclampsia disappeared between Chinese and White groups.[47]

Considering the observation that Black women had the highest rates of preeclampsia, while other races and ethnicities had inconsistent associations, or even negative associations, with preeclampsia, the question is then begged, why different minority groups have different experiences of disease, if one applies the framework of racism and discrimination as a determinant of health. One possibility is that racism and discrimination is not experienced similarly by different minorities. Interestingly, in a study of three racial groups (Asian Americans, Latino-American, and Afro-Caribbean American), the Afro-Caribbean group was the most likely to report perceived discrimination,[93] suggesting that racism is a sociocultural construct that is rooted in the specific context and historical circumstances of the minority group involved.

Perhaps the most novel and well-supported finding of this review is that women living in neighbourhoods characterized by lower socioeconomic status experienced higher odds of preeclampsia compared to women living in wealthier neighbourhoods. The findings of this study are consistent with recent cardiovascular health research showing that socioeconomic inequalities are associated with higher prevalence of disease and mortality.[94,95] Differences observed could be explained by several pathways. Firstly, poorer neighbourhoods may have inadequate access to healthcare, which could exacerbate chronic underlying heart disease processes that may put a woman at higher risk of preeclampsia during pregnancy. Indeed, it has been shown that women living in lower socioeconomic areas had higher odds of CVD compared with women from more affluent areas.[96] This explanation, however, is insufficient because not all women with

preeclampsia living in poor areas accordingly have a CVD comorbidity. To further elucidate the relationship, future research should assess the mediating factors of socioeconomic disparities and preeclampsia, such as investigating whether the higher preeclampsia incidence in more deprived neighbourhoods remains after adjusting for cardiovascular risk and access to medical care.

A systematic review of immigrant status and pregnancy-related hypertensive disorders of pregnancy found that women who immigrated were at a lower risk of hypertensive disease relative to women who were native to the country. This was in accordance with our finding that immigrant status was protective against preeclampsia. The two exceptions in our analysis were studies looking at immigrant subgroups who may not represent wealthier groups and who immigrate out of necessity, such as asylum seekers[65] and refugees.[69] These outliers are consistent with the 'healthy immigrant effect,' proposed to explain the apparent paradox that immigrants tend to have better health than non-immigrants.[97] Healthy individuals who are physically and financially robust may self-select to immigrate to another country, and thus health comparisons with the non-immigrant population show superior health in the former group.[97,98]

Strengths

A strength of this review is its comprehensive nature. We synthesized the available epidemiological evidence relating a large scope of the SDOH to preeclampsia. Providing a single study that addresses these relationships can be used as a starting point for social epidemiologists as well as clinicians and scientists invested in better understanding preeclampsia beyond the biomedical model. An addition strength is the consistency and transparency of the systematic review methodology. The search strategy was developed with a librarian, and it is likely that the breadth of social determinants in relation to preeclampsia were captured in the search. Upon conception of the methodology, the review protocol was examined by all the authors and published in a review registry. Dual review at the screening of papers, data extraction, and quality assessment phases was done to reduce bias throughout the process.

Through iterative processes in this review, we have separated, and made the distinction between, socioeconomic status on the neighbourhood level, and other social determinants on the individual level, because whereas the former is rooted in population-level, upstream inequities, the latter reflects more direct, individualistic or community-based determinants.[99] The decision to make this distinction was made due to similarities in measuring and operationalizing the various

SDOH in the included papers, and may provide a clearer, more concise image of the relationship between neighborhood deprivation and preeclampsia. This relationship has been examined explicitly in CVD inequity research.[94,96,100]

Limitations

A possible limitation of this systematic review is its breadth in study inclusion. Although it captured much of the available literature by searching in Ovid databases, CINAHL, and Sociological Abstracts, it did not include the Web of Science database, and so some studies may have been missed in the keyword search stage. In terms of inclusion of studies, we followed Campbell and Cochrane Equity Methods Group's recommendation to stratify preeclampsia outcome by the PROGRESS-Plus framework.[101] Although extensive, this framework does not cover the full spectrum of SDOH, and some articles that chose to define social determinants differently (e.g., "booking status" in prenatal care[102] or insurance status[103]) were excluded. That being said, by providing a range of determinants that encompass several facets of social and material deprivation, and by limiting these to a standardized framework, we were able to synthesize and manage the evidence more coherently.

Another important limitation of this review is that we did not address intersectionality of SDOH. For example, although we found socioeconomic status to be significantly associated with preeclampsia, we do not know how these effects interact with race/ethnicity to produce higher disparities in disease. Future work in this field should aim to characterize how effects may be modified when considering women with multiple socioeconomic risk factors.

2.5 Conclusion

The current literature appraised in this systematic review suggests that Black race, Native race, education, socioeconomic status, and marital status are positively and significantly associated with preeclampsia. Subgroup analyses showed that the direction of association with Hispanic ethnicity varies according to geographical region. Less clear are the risks associated with rural residence, religion, Asian ethnicity, and employment status. Future perinatal health research should aim to complement the existing literature by assessing the under-studied determinants mentioned above, as well as aim to elucidate the pathway of how experiences of deprivation lead to this placental disease of pregnancy. These findings provide an insight into how social

inequalities may translate into physical manifestations of disease, and may better equip healthcare workers with evidence to reduce inequalities in maternal and fetal health outcomes.

No funding sources to disclose

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CHAPTER 3: The Social Determinants of Preeclampsia: a Population-based Cohort Study in Alberta

3.1 Introduction

Preeclampsia is a hypertensive disease of pregnancy marked by new-onset hypertension and proteinuria, or other signs of organ damage, after 20 weeks of gestation.[1,2] Although the delivery of the placenta marks resolution of the disease, preeclampsia incurs systemic endothelial damage and contributes to life-long cardiovascular disease (CVD) risk for the mother as well as the baby.[3] A meta-analysis of longitudinal data has shown that after a little more than a decade of mean follow-up, pregnancies complicated by preeclampsia were associated with almost a 4-fold relative risk (RR) of hypertension, and about a two-fold risk of ischemic heart disease and stroke.[4] Neonates have increased risk of being preterm,[5] and small for gestational age (SGA) as a consequence.[6] Stillbirth rate per 1,000 pregnancies was found to be 5.6 in pregnancies with preeclampsia, compared to 3.6 in normotensive ones.[7] Additionally, there is some evidence showing that the deprived placental environment during pregnancy may lead to increased risk of disease such as hypertension and stroke later in the life of the child.[8,9]

There is increasing evidence demonstrating a relationship between the social determinants of health (SDOH) and adverse pregnancy and birth outcomes such as intrauterine growth restriction (IUGR), preterm birth, stillbirth, and infant mortality.[10] The SDOH include factors such as income, area of residence, education, unemployment, food insecurity, housing, social exclusion, and race.[11] Referred to as the "causes of the causes",[12] SDOH are upstream factors and processes that affect a person's health status, and may be the fundamental, underlying instigators of many diseases. Beyond individual characteristics and behaviours such as quality of diet, smoking, and genetic disposition, SDOH pertain to people's living conditions as well as their quality of interactions in everyday life. More than absolute conditions, SDOH also describe how differences in health states and outcomes can be explained by inequalities in people's relative socioeconomic status (SES).[11]

To date, studies of the SDOH in relation to preeclampsia have focused on a plethora of salient predictors. In the United States, for example, clear inequalities in preeclampsia incidence and outcomes were demonstrated between African-American and Caucasian women,[13-15] although the disparity was not as consistent among Hispanic women.[14,16-18] In most studies, highly

heterogeneous Asian ethnicities have been grouped together under one category, making it difficult to decipher trends in these ethnically-distinct groups.[14,17,19,20] In addition to ethnicity, neighbourhood-level indicators point to disparities in preeclampsia. Women in the lowest quintiles of SES experienced higher rates of preeclampsia in China,[21] Norway,[22] Netherlands,[23] New Zealand,[24] and the United States.[25]

Despite the emerging evidence in the U.S. and other countries, there is a dearth of information of how the SDOH are related to preeclampsia in Canada. Out of 220 studies reviewed for inclusion in a systematic review of preeclampsia and SDOH in a forthcoming review of the literature (see Chapter 2 of this thesis), only two[26,27] were conducted in Canada. Filling the knowledge gap is important to decipher if, in a country with universal healthcare, there still exists inequalities in health according to a person's social and economic circumstances. Identifying these demographic and contextual risk factors is also important because Canada is a diverse country: geographically, ethnically, and socially. Examining the relationships between how people live and the effects this has on their risk of disease during pregnancy can offer valuable information for public health workers, clinicians, and policy makers. As well, considering the risks associated with preeclampsia on the long-term cardiovascular health of the mother and the child, identifying high risk populations in preeclampsia research can have far-reaching benefits. The purpose of the present investigation is to examine the association between maternal ethnicity, immigrant status, rural residence, marital status, and social and material deprivation, and preeclampsia in a population-based longitudinal pregnancy and birth cohort in Alberta. A secondary objective is to examine whether material deprivation is associated with adverse obstetrical and neonatal health outcomes among women with preeclampsia.

3.2 Methods

3.2.1 Data source and linkage

Pregnancy and birth data were obtained from administrative health service data records that include detailed maternal demographics; clinical and obstetrical outcomes; delivery information; and maternal and neonatal clinical data. The Alberta Pregnancy and Birth Cohort database was developed by linking the following data: (1) Ambulatory care visits, inpatient hospital separations, and practitioner claims, which provided pertinent clinical history and healthcare utilization data; (2) Central Stakeholder Registry which provided information about

earliest previous country if immigration had occurred; (3) the Population Registry, which was used to determine Alberta residency, as well as provided information on maternal date of birth and postal code; (4) live births data through the Vital Statistics Birth File data which was used to link maternal and baby files (5) Pampalon's Material and Social Deprivation Indices, which are based on the 2006 census data from Statistics Canada.[28] Data were linked using de-identified personal health identifiers.

3.2.2 Study Design and Population

This retrospective cohort study included all women who had a live, singleton birth in the province of Alberta, Canada, between January 1, 2005 to December 31, 2014. Pregnancies of gestational age less than 23 weeks, and of women who were not residents of Alberta (i.e. not registered in the Alberta Health Care Insurance Plan) or who resided outside of Alberta in the fiscal year of birth, were excluded. The unit of interest was pregnancy, so women could be represented more than once in the dataset. Potential clinical characteristics that were considered as risk factors for preeclampsia were maternal age, parity, prior CVD, hypertension, gestational diabetes mellitus (GDM), and pre-existing diabetes mellitus (see Appendix 8 for International Classification of Disease, tenth revision (ICD-10) diagnosis codes). Missing exposure data for independent variables were coded as separate categories for each variable.

3.2.3 Data definitions

Preeclampsia/eclampsia

The outcome of interest was preeclampsia or eclampsia diagnosis. Diagnoses and procedures were identified based on ICD-10 codes.[29] These diagnoses are recorded as part of the hospitalization record at delivery. We defined preeclampsia as ICD-10 codes O11, O14 and O15 to capture chronic hypertension superimposed on preeclampsia, preeclampsia, and eclampsia diagnoses, respectively.[29] The definition of preeclampsia is pregnancy-induced hypertension (or pre-existing hypertension in the case of code O11) with significant proteinuria or evidence of end-organ damage including hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome. Eclampsia is defined as convulsions associated with pregnancy, labour, or the puerperium.[30] Gestational hypertension was not included in the definition of preeclampsia-eclampsia as it is considered a distinct group of hypertensive disorders during pregnancy, and preeclampsia has an epidemiological, etiological, risk factor, and morbidity profile unique from

it.[30-33] A preeclampsia or eclampsia combined outcome variable was created, henceforth referred to as 'preeclampsia'.

Clinical factors

Maternal age was calculated as the difference between the year of delivery obtained from the Vital Statistics Birth Registry and the woman's year of birth recorded in the Population Registry.[34] Maternal age was categorized into four groups: <20, 20-34, 35-40 and >41 years of age. The reference category was the age group 20-34. Parity was defined as nulliparous (first pregnancy) or multiparous (subsequent pregnancy). Pre-existing conditions were obtained from maternal inpatient hospitalization files which contain a main diagnosis and 24 secondary diagnoses. Inpatient and outpatient prior conditions, including cardiovascular disease and hypertension, diagnosed 270 days prior to delivery, were grouped together in a multi-level variable (CVD only, both CVD and hypertension, or neither). Pre-existing diabetes mellitus, as well as GDM at the time of delivery, were also included as important clinical factors in the analysis, as these comorbidities are known risk factors of preeclampsia. See appendix 8 for diagnosis codes.

Rural residence

We linked the maternal 6-digit postal codes at the time of delivery with the postal code conversion files (PCCF) based on the 2006 Census.[34,35] The PCCF is used to associate the Canada Post Corporation postal codes with Statistics Canada's census-derived standardized geographic areas. The PCCF attaches each postal code with a statistical area classification that groups areas based on the degree of urbanity, with census metropolitan areas (CMAs) and Census Agglomerations (CAs) considered as the most urban. Census subdivisions are categorized based on the degree of metropolitan influence, which is based on the proportion of residents in the geographic area that commute to a metropolitan area for work. Strong, moderate, weak, and no metropolitan influence zones correspond to proportions of ≥ 30%, 5%–29%, 1%–5% and <1%, respectively.[34] Census metropolitan areas, census agglomerations, and census subdivisions with strong metropolitan influence were categorized as urban in our study. Census subdivisions with moderate, weak, or no metropolitan influence were categorized as rural. Our rationale, similar to that of Lisonkova and colleagues in their British Columbia study of maternal health outcomes in rural and urban areas,[36] is that areas that are strongly influenced by urban areas will have the

healthcare accommodations and lifestyles that are similarly available to the urban areas. If area type was missing for a postal code (N=6758, or 1.4%), then rural area was determined based on the presence of a '0' in the second digit of the postal code, which is an indicator of a rural delivery site for Canada Post.[37]

Marital status at time of birth

Marital status at time of birth was obtained from the birth registry. Due to a change in data collection protocol legislation in 2012, women are routinely asked at the time of registering their child's birth to report their marital status as either 'legally married' or 'not legally married'. Prior to 2012, other categories included 'legally married and father is the biological father', 'legally married and father is not the biological father', or 'not legally married', which includes never married, cohabiting, divorced, or widowed. Because of the change in the definition, marital status of women whose husband was or was not the father of the child were grouped under one category of 'Married', and women whose status was 'Not legally married' were categorized as unmarried. Statuses categorized as 'unknown', entered as an invalid number, or had a missing value were categorized as 'Missing'. Married status was defined as the reference group.

Ethnicity

According to the 2016 Census, 23.5% of Albertans self-identified as non-Caucasian visible minorities.[38] The largest ethnic minorities were South Asian (24.7%), Chinese (17.0%), and Filipino (17.8%).[38] In our study, ethnicity was based on a combination of highly predictive Chinese and South Asian surname algorithms that were previously validated from the Institute for Clinical and Evaluative Sciences (ICES).[39] Earliest maternal surname available in the stakeholder registry was used. Women were categorized as 'General Population' if their records did not indicate an ethnicity captured by the algorithms.

We also used an additional data source, previous country of residence, to separately assess ethnicity in order to complement the algorithm's interpretation, as well as to add the category of Filipino ethnicity, an important minority in Alberta. If previous country was listed as 'China' women were categorized as 'Chinese'; an indication of 'Philippines' was categorized as Filipino; 'India', 'Pakistan', 'Bangladesh', 'Nepal', 'Bhutan', 'Maldives' or 'Sri Lanka' were categorized

as ‘South Asian’; finally, all other countries were categorized as ‘Other ethnicity’, and those without a previous country of residence were considered ‘General population’.

Immigrant status

Immigrant status was defined as a binary variable based on the presence or absence of a previous country of residence from the Central Stakeholder Registry.

Material and social deprivation

The postal codes were used to link the Pregnancy Birth Cohort to the 2006 Canadian Deprivation Index data to incorporate neighborhood-level information on social and material deprivation, a measure of socioeconomic status (SES).[28] Since our cohort extended between 2005-2014, we chose to use the 2006 version of the Canadian Deprivation Index, which was the last mandatory Census in Canada during our study period. Region-specific (i.e. Alberta and the Prairies) deprivation indices were utilized to categorize women from most privileged (quintile 1) to least privileged (quintile 5). Material deprivation is composed of indicators such as low income and education and low employment to population ratio, whereas social deprivation consists of being separated, divorced, or widowed, living in a single-parent family, or living alone.[28] Unmatched cases resulting from postal codes that were missing, invalid, incorrect, or that were not part of the postal code conversion file, were coded as ‘0’ to indicate ‘Missing’.

Secondary outcomes

To assess whether, among women with preeclampsia, low SES is associated with worse maternal and neonatal outcomes, a preeclampsia sub-cohort analysis was undertaken, using the material deprivation index quintiles as a proxy for SES. Maternal outcomes included Caesarian section and induction use. Neonatal outcomes included preterm delivery (defined as <37 weeks of gestation), small for gestational age (SGA), large for gestational age (LGA), and neonatal intensive care unit (NICU) stay. An infant was categorized as SGA or LGA if their birth weight was at or below the 10th percentile for the former, and at or above the 90% percentile for the latter, from a distribution of infants of the same sex and gestational age.[40]

3.2.4 Statistical Analysis

Frequencies and percentages were computed for all variables. In the exploratory data analysis stage, to assess collinearity, relationships between categorical variables were assessed using Chi-square tests and variables with a Cramer's coefficient >0.8 were deemed highly correlated. Among highly correlated variables, the more clinically relevant factor was selected. We examined the association between SDOH variables and the prevalence of preeclampsia in a sequence of logistic regression models: first we examined the univariate association between each SDOH variable and preeclampsia; next we examined these associations after adjusting for age and parity; and finally after adjusting for pre-existing disease. The associations were reported as odds ratios (ORs) with 95% confidence intervals (CIs). All significance levels were assessed at an alpha cut-off value of 0.05. The generalized estimated equation (GEE) approach was used to account for multiple deliveries per woman present in the longitudinal cohort, with the maternal ID number as the clustering variable.

For the second part of the study, perinatal and neonatal outcomes among women diagnosed with preeclampsia were compared between women who were either socioeconomically advantaged or disadvantaged according to their Pampalon material deprivation index. Quintile 1, the highest socioeconomic group, was used as the reference group to quintiles 2-5. A 'missing' group was additionally added for those women whose postal code did not link with the Pampalon deprivation index We examined both the univariate and age-adjusted association between social and material deprivation and perinatal and neonatal outcomes which are reported as OR with 95% CI. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc.).

3.3 Results

Our study included 487,938 live births that took place in Alberta between 2005-2014. After excluding deliveries resulting in multiple (twins, triplets, etc.) births (N= 16,467), deliveries of women who were not residents of Alberta (N= 5,583), pregnancies with missing or invalid information such as gestational age, birthweight, or fetal sex (N= 248), and deliveries with gestational age less than 23 weeks, (N=695) our final cohort consisted of 473,143 singleton live births of 311,851 mothers. Full information was obtained for all the explanatory variables except

the marital status (0.2% missing) and the social and material deprivation indices (5.3% missing). Figure 3.1 provides the patient flow diagram.

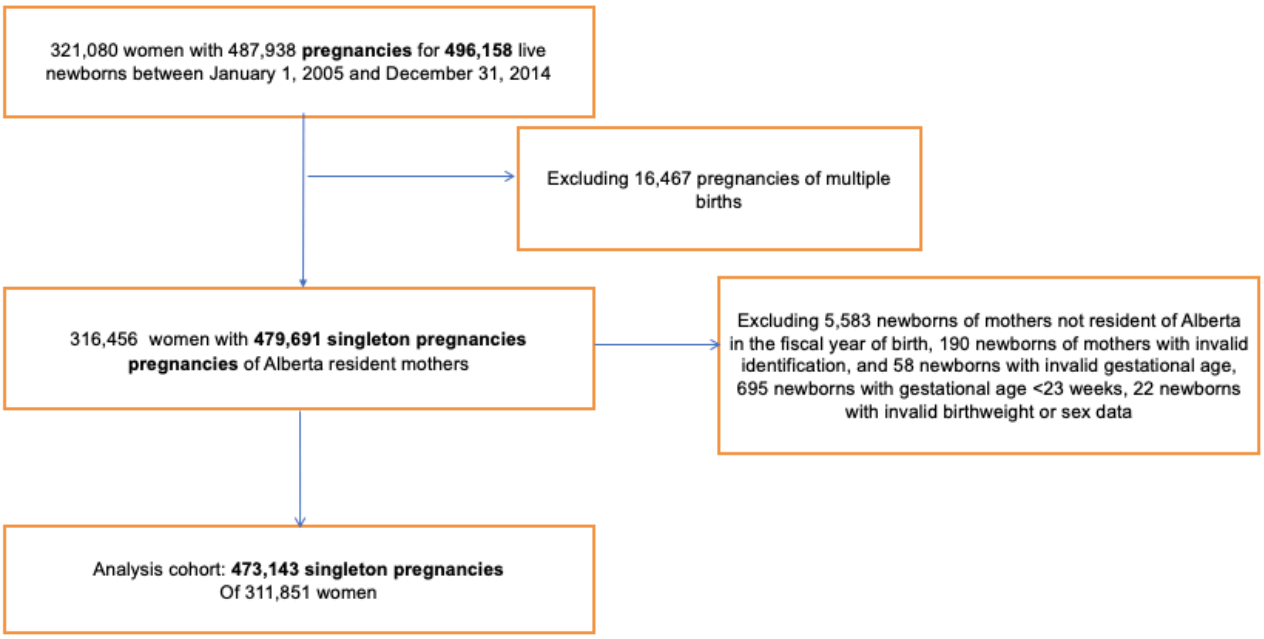

Figure 3.1: Cohort selection flowchart

The baseline characteristics of the women included in the final study cohort are presented in Table 3.1. The largest proportion of women were in between 20-35 years of age (78.1%) and a majority were nulliparous (65.5%). Rates of pre-existing cardiovascular disease and hypertension (1.1%) and diabetes mellitus (3.2%) were low. Overall, 9% of the cohort had GDM. The majority lived in urban areas (81.2%) and were married (70.3%) at the time of delivery. Women with Chinese ethnicity represented 3.4% of our cohort, while South Asians comprised 2.9%. In terms of socioeconomic status, 23.2% of the women were in the highest quintile of material deprivation and 14.2% had the lowest quintile of material deprivation. The proportion of women was somewhat evenly distributed across the quintiles of social deprivation.

In our study population, the overall prevalence of preeclampsia and eclampsia was 1.46% (N=6,897). Upon a correlation analysis, no variables had a high Cramer's V value above the cut-off value, and so no collinearity between the variables was established. As shown in Table 3.1, compared to women without preeclampsia, women with preeclampsia were overrepresented in the youngest (3.3% versus 5.0%) and oldest (2.1% versus 3.3%) age groups, and were more likely to

be nulliparous (65.3% versus 81.6%). The rates of pre-existing CVD or hypertension were 0.1% among women without preeclampsia compared to 1.1% in women in the preeclampsia group. Similarly, women with preeclampsia had an almost two times higher rate of pre-existing diabetes, and a six-times higher rate of GDM than among women without preeclampsia. Women with preeclampsia were more often living in rural areas (23.1% vs. 18.7%) and unmarried (33.8% versus 29.5%), but were less likely to be Chinese (1.8% versus 3.4%), South Asian (2.5% versus 2.9%) or an immigrant (16.7% versus 18.9%). Although there was not a distinct pattern across the five quintiles of the social deprivation index, women with preeclampsia were slightly less likely to be in the most well-off material quintile (20.3% versus 23.3%) and slightly more likely to be in the lowest quintile (15.0% versus 14.1%).

Table 3.1: Characteristics of women who gave birth in Alberta between 2005-2014, stratified by delivery complicated by preeclampsia

Variable	Variable category	Total N (%)	No preeclampsia N (%)	Preeclampsia N (%)
Total		473143	466246 (98.54)	6897 (1.46)
Age group	**12-19**	15727 (3.3)	15384 (3.3)	343 (5.0)
	20-34	369583 (78.1)	364482 (78.2)	5101 (74.0)
	35-40	77902 (16.5)	76680 (16.4)	1222 (17.7)
	41-54	9931 (2.1)	9700 (2.1)	231 (3.3)
Nulliparous		309978 (65.5)	304352 (65.3)	5626 (81.6)
Previous cardiovascular disease or hypertension	No	467988 (98.9)	461254 (98.9)	6734 (97.6)
	CVD only	4649 (1.0)	4562 (1.0)	87 (1.3)
	Both hypertension and CVD	506 (0.1)	430 (0.1)	76 (1.1)
Gestational Diabetes Mellitus		23867 (5.0)	23248 (5.0)	619 (9.0)
Previous Diabetes Mellitus		2772 (0.6)	2551 (0.5)	221 (3.2)
Rural residence		88905 (18.8)	87315 (18.7)	1590 (23.1)
Married status	Married	332505 (70.3)	327970 (70.3)	4535 (65.8)
	Not married	139688 (29.5)	137354 (29.5)	2334 (33.8)
	Missing	950 (0.2)	922 (0.2)	28 (0.4)
Ethnicity (surname)	Chinese	16110 (3.4)	15988 (3.4)	122 (1.8)
	South Asian	13502 (2.9)	13328 (2.9)	174 (2.5)

	General population	443531 (93.7)	436930 (93.7)	6601 (95.7)
Ethnicity (previous country)	Chinese	5924 (1.3)	5886 (1.3)	38 (0.6)
	South Asian	15182 (3.2)	15016 (3.2)	166 (2.4)
	Filipino	10983 (2.3)	10686 (2.3)	297 (4.3)
	Other	57272 (12.1)	56621 (12.1)	651 (9.4)
	General population	383782 (81.1)	378037 (81.1)	5745 (83.3)
Immigrant status		89361 (18.9)	88209 (18.9)	1152 (16.7)
Material Deprivation Index	1 (high SES)	109884 (23.2)	108481 (23.3)	1403 (20.3)
	2	100059 (21.1)	98611 (21.1)	1448 (21.0)
	3	94345 (19.9)	92985 (19.9)	1360 (19.7)
	4	76841 (16.2)	75623 (16.2)	1218 (17.7)
	5 (low SES)	66962 (14.2)	65928 (14.1)	1034 (15.0)
	Missing	25052 (5.3)	24618 (5.3)	434 (6.3)
Social Deprivation Index	1 (high SES)	77242 (16.3)	76208 (16.3)	1034 (15.0)
	2	94747 (20.0)	93415 (20.0)	1332 (19.3)
	3	104285 (22.0)	102790 (22.0)	1495 (21.7)
	4	89749 (19.0)	88361 (19.0)	1388 (20.1)
	5 (low SES)	82068 (17.3)	80854 (17.3)	1214 (17.6)
	Missing	25052 (5.3)	24618 (5.3)	434 (6.3)

The burden of adverse maternal and neonatal health outcomes was higher among women with preeclampsia than without preeclampsia for all outcomes except LGA, with a marked increase in the likelihood of Caesarian section (53.7% versus 26.4%), induction (60% versus 25.1%), preterm delivery (37.7% versus 6.3%), SGA (20.8% versus 9.0%) and NICU stay for more than one day (40.1% versus 10.6%) (see Table 3.2).

Table 3.2: Maternal and neonatal adverse outcomes of those with and without preeclampsia in the cohort of 2005-2014 Alberta deliveries

Outcome	**Total N (%)**	**No preeclampsia N (%)**	**Preeclampsia N (%)**	**p-value (2 sided)**
Total N	473143	466246	6897	
Caesarian section	126680 (26.8)	122973 (26.4)	3707 (53.7)	<.0001
Induction	120953 (25.6)	116816 (25.1)	4137 (60.0)	<.0001
Preterm	32015 (6.8)	29418 (6.3)	2597 (37.7)	<.0001
SGA	43448 (9.2)	42010 (9.0)	1438 (20.8)	<.0001
LGA	44991 (9.5)	44340 (9.5)	651 (9.4)	0.8416
NICU stay	52319 (11.1)	49551 (10.6)	2768 (40.1)	<.0001

Univariate logistic regression showed that all exposure variables were significantly ($p<0.05$) associated with preeclampsia, except for social deprivation index (see Table 3.3). In terms of clinical and demographic variables, women in the youngest and oldest age groups, women with primiparous deliveries, and deliveries of women with pre-existing CVD, hypertension, or diabetes, were associated with the highest odds of preeclampsia in this cohort.

Table 3.3 presents the following: the unadjusted (univariate) association between baseline characteristics and the incidence of preeclampsia; the association between SDOH variables and preeclampsia after adjusting for age and parity; and the association between SDOH variables and preeclampsia after adjusting for age, parity, and pre-existing conditions, and GDM. Univariate analysis showed that compared to women living in urban residence, women in rural residence had 31% increased odds of preeclampsia (OR=1.31, 95% CI: 1.24-1.39), but this increased to 40% increased odds (adjusted OR (aOR) =1.40, 95% CI: 1.32-1.48) after adjustment for age, parity, and previous conditions, suggesting one or more of the variables led to negative confounding. In contrast, the unadjusted odds of 1.24 (95% CI: 1.17-1.30) associated with being unmarried at the time of delivery decreased to an aOR of 1.15 (95% CI: 1.09-1.22) after maximal adjustment. Women whose marital status was missing had a maximally-adjusted aOR of 2.22 (95% CI: 1.52-3.26) for preeclampsia compared to married women.

Chinese women had the lowest unadjusted odds of preeclampsia compared to the general population (OR=0.50, 95% CI: 0.42-0.60). Adjustments by age and parity and prior conditions further decreased the magnitude of this association (aOR=0.45, 95% CI: 0.38-0.54) compared to women in the general population. Although not as marked, a similar pattern was observed in South Asian women: unadjusted OR= 0.86 (95% CI: 0.73-1.00 and aOR=0.79, 95% CI: 0.67-0.92. Using previous country to determine ethnicity, similar findings were observed for Chinese and South Asian women. An additional ethnicity category identified through the previous country variable was Filipino, which had a 52% increased odds (aOR=1.52, 95% CI: 1.35-1.72) of preeclampsia after taking into consideration age, parity, and previous risk factors.

Overall, immigrant status was associated with decreased unadjusted odds of preeclampsia (OR=0.86, 95% CI: 0.80-0.91), and this association was strengthened after adjustment for age and parity (aOR=0.81, 95% CI: 0.75-0.86), as well as pre-existing hypertension, CVD, diabetes and GDM (aOR=0.79, 95% CI: 0.74-0.85). Material deprivation quintiles showed that lower SES (quintiles 2-5) had higher odds of preeclampsia compared to the highest SES group (quintile 1),

although no clear incremental pattern was observed. Social deprivation quintiles did not show a clear significant association. However, similar to marital status, the missing categories of both material and social indices had the largest preeclampsia risk.

Table 3.3: Odds ratios showing associations between the social determinants of health and preeclampsia in an Alberta 2005-2014 birth and pregnancy cohort

Characteristic	Univariate OR (95% CI)	Model 1 aOR (95% CI)*	Model 2 aOR (95% CI)**
Age group			
12-19	1.60 (1.43-1.78)		
20-34 (reference)	1.00		
35-40	1.13 (1.06-1.20)		
41-54	1.67 (1.46-1.90)		
Nulliparous	2.28 (2.15-2.42)		
Previous cardiovascular disease or hypertension			
None	1.00		
CVD only	1.29 (1.03-1.61)		
Both hypertension + CVD	11.4 (8.71-14.8)		
Gestational Diabetes Mellitus	1.82 (1.67-1.99)		
Previous Diabetes Mellitus	5.87 (5.07-6.80)		
Rural vs. Urban residence (reference: urban residence)	1.31 (1.24-1.39)	1.40 (1.32-1.48)	1.40 (1.32-1.48)
Married status			
Married	1.00	1.00	1.00
Not Married	1.24 (1.17-1.30)	1.15 (1.09-1.22)	1.15 (1.09-1.22)
Missing	2.17 (1.50-3.15)	2.25 (1.54-3.28)	2.22 (1.52-3.26)
Ethnicity (surname)			
General population	1.00	1.00	1.00
Chinese	0.50 (0.42-0.60)	0.46 (0.38-0.55)	0.45 (0.38-0.54)
South Asian	0.86 (0.73-1.00)	0.82 (0.70-0.96)	0.79 (0.67-0.92)
Ethnicity (previous country)			
General population	1.00	1.00	1.00
Chinese	0.43 (0.31-0.59)	0.38 (0.27-0.52)	0.37 (0.27-0.51)
South Asian	0.72 (0.61-0.84)	0.70 (0.60-0.82)	0.66 (0.56-0.78)
Filipino	1.81 (1.61-2.05)	1.59 (1.41-1.80)	1.52 (1.35-1.72)
Other ethnicity	0.75 (0.69-0.82)	0.72 (0.66-0.78)	0.72 (0.66-0.79)
Immigrant status	0.86 (0.80-0.91)	0.81 (0.75-0.86)	0.79 (0.74-0.85)
Material Deprivation Index			
1 (highest)	1.00	1.00	1.00
2	1.13 (1.05-1.22)	1.16 (1.07-1.25)	1.15 (1.06-1.24)
3	1.13 (1.05-1.22)	1.16 (1.07-1.25)	1.14 (1.05-1.23)
4	1.25 (1.15-1.35)	1.28 (1.18-1.38)	1.25 (1.15-1.35)

5 (lowest)	1.22 (1.12-1.32)	1.26 (1.16-1.37)	1.22 (1.12-1.33)
Missing	1.35 (1.21-1.50)	1.43 (1.28-1.59)	1.40 (1.25-1.56)
Social Deprivation Index			
1 (highest)	1.00	1.00	1.00
2	1.05 (0.96-1.13)	1.03 (0.95-1.12)	1.02 (0.94-1.11)
3	1.07 (0.99-1.16)	1.04 (0.96-1.13)	1.04 (0.96-1.13)
4	1.16 (1.07-1.25)	1.11 (1.02-1.20)	1.09 (1.01-1.19)
5 (lowest)	1.11 (1.02-1.20)	1.02 (0.94-1.11)	1.01 (0.92-1.09)
Missing	1.28 (1.14-1.43)	1.29 (1.15-1.44)	1.27 (1.13-1.42)

aOR=adjusted odds ratio, CVD=cardiovascular disease
*Model 1 adjusted each individual SDOH for age group and parity
**Model 2 adjusted further for pre-existing hypertension or cardiovascular disease and diabetes (GDM and DM)

We used deliveries with preeclampsia (N=6,897) to examine the association between material deprivation and adverse pregnancy outcomes. Rates of adverse pregnancy outcomes across material deprivation categories are presented in Table S1 of Appendix 7. Table 3.4 shows unadjusted and age-adjusted associations between each material deprivation quintile (compared to quintile 1 as the reference category) and adverse outcomes. There was no statistically significant association between material deprivation and Caesarian section, preterm, SGA, or NICU stay. There was a marginally significant increase in the odds of induction with decreasing material deprivation, which remained even after adjustment for age. There was no association between material deprivation and SGA births. In contrast, women in the lowest material deprivation quintile had a 43% higher unadjusted risk of LGA (OR=1.43, 95% 1.08-1.88) which attenuated to 36% (aOR=1.36, 95% CI: 1.03-1.79) after adjusting for maternal age. Once again, women with missing data had the highest risk of adverse outcomes, with 61% (aOR=1.61, 95% CI: 1.14-2.27) increased odds of an LGA birth compared to the highest quintile group (Table 3.4).

Table 3.4: Crude and adjusted odds ratios and 95% confidence intervals of material deprivation quintiles and maternal outcomes among a sub-cohort of women with preeclampsia

	Material Deprivation Quintile				
	2	3	4	5 (low)	Missing
Unadjusted Associations					
Caesarian section	1.09 (0.94-1.27)	1.06 (0.92-1.23)	1.01 (0.87-1.18)	0.91 (0.78-1.07)	1.03 (0.83-1.27)
Induction	0.90 (0.77-1.05)	0.85 (0.73-0.99)*	0.84 (0.71-0.98)*	0.84 (0.71-0.99)*	0.80 (0.64-1.00)
Preterm	1.02 (0.88-1.19)	0.95 (0.81-1.11)	0.82 (0.70-0.96)*	0.92 (0.78-1.08)	1.05 (0.84-1.31)

SGA	0.96 (0.80-1.14)	0.90 (0.75-1.08)	0.93 (0.77-1.12)	0.88 (0.72-1.07)	0.84 (0.64-1.10)
LGA	1.10 (0.85-1.44)	1.18 (0.90-1.54)	1.18 (0.90-1.56)	1.43 (1.08-1.88)*	1.65 (1.17-2.32)*
NICU stay	1.08 (0.93-1.26)	1.13 (0.97-1.31)	1.00 (0.85-1.17)	1.00 (0.85-1.18)	1.01 (0.81-1.26)
Associations after adjusting for maternal age					
Caesarian section	1.12 (0.97-1.30)	1.10 (0.95-1.28)	1.05 (0.90-1.22)	0.98 (0.83-1.16)	1.09 (0.87-1.35)
Induction	0.89 (0.76-1.03)	0.82 (0.71-0.96)*	0.82 (0.70-0.96)*	0.81 (0.68-0.96)*	0.77 (0.61-0.96)*
Preterm	1.06 (0.91-1.23)	0.99 (0.85-1.16)	0.86 (0.73-1.01)	1.02 (0.86-1.21)	1.13 (0.90-1.42)
SGA	0.96 (0.81-1.15)	0.91 (0.76-1.10)	0.94 (0.78-1.14)	0.91 (0.74-1.11)	0.85 (0.65-1.12)
LGA	1.10 (0.84-1.43)	1.17 (0.89-1.53)	1.17 (0.88-1.54)	1.36 (1.03-1.79)*	1.61 (1.14-2.27)*
NICU stay	1.11 (0.96-1.30)	1.18 (1.01-1.37)	1.04 (0.89-1.22)	1.09 (0.92-1.28)	1.07 (0.86-1.34)

Reference group for all estimates is quintile 1, the highest socioeconomic level
*Statistically significant ($p<0.05$)

3.4 Discussion

In this large, province-wide, retrospective cohort study, we utilized population data to assess the independent association between social determinants including rural residence, ethnicity, immigrant status, marital status, neighbourhood-level material and social deprivation, and preeclampsia. We also investigated if material deprivation among women with preeclampsia is associated with worse obstetrical and neonatal outcomes.

The overall prevalence of preeclampsia among singleton deliveries in our Alberta cohort between 2005 and 2014 was 1.46%. This is on the lower end of measurements reported in industrial countries (1.4%-4.0%).[41] Consistent with current knowledge, the highest risk groups were women in the extreme ends of age groups, nulliparous women, women with pre-existing hypertension and CVD,[42] pre-existing diabetes, and women with GDM. It has been reported that preeclampsia is diagnosed in 5-20% of women with type 1 diabetes,[43,44] and 10-14% with type 2 diabetes.[43-46] This association signals that either the metabolic processes in both diabetes types catalyzes preeclampsia in pregnancy, or that these two diseases have a common pathophysiological origin.

Knowing the clinical risk factors of preeclampsia, and recognizing that low SES groups tend to have a higher prevalence of these risk factors, this study attempted to discern whether social

and economic determinants were linked to preeclampsia, after accounting for these clinical determinants.

This study had several key findings, one of which is that, despite universal healthcare, women in rural areas had a 40% higher risk (aOR=1.40, 95% CI: 1.32-1.48) of preeclampsia compared to women living in urban areas. Previous data has shown that in Canada (excluding Quebec), 18% of all in-hospital deliveries are of women from rural areas, making rural residence a pertinent determinant of health and disease during pregnancy.[47] Our findings are similar to findings of a Korean study that showed women living in rural areas had a 29% increased risk of preeclampsia compared to those living in metropolitan areas (aOR 1.29, 95% CI 1.11-1.48).[48] However, a population cohort study set in British-Columbia found that preeclampsia was not significantly more common among rural dwellers, but did find that rural residence was associated with 2.45 times the odds of eclampsia, the exacerbated, life-threatening form of preeclampsia, compared to urban residence (aOR 2.45; 95% CI 1.59-3.77).[36] Although several studies looked at rural residence in the context of adverse birth outcomes,[49-52] more research is needed to clarify the link between rural residence and maternal outcomes, including preeclampsia and eclampsia.

Another key finding was that women who were not married at the time of delivery had a 24% increased risk of preeclampsia (OR 1.24, 95% CI 1.17-1.30). This risk was attenuated to 15% (aOR 1.15, 95% CI 1.09-1.22) after adjustment for the other pertinent demographic and clinical variables. Marital status has been found to be protective for preeclampsia in several other studies. In a Washington study of early- and late-onset preeclampsia, unmarried women had 14% increased adjusted hazard risk (aHR 1.14, 95% CI 1.10-1.19) of preeclampsia.[53] Two cross-sectional studies, one set in Ethiopia,[54] and one that pooled data from 23 lower-income countries,[55] reported similar findings. Drawing from studies looking at outcomes other than preeclampsia, a 2018 Canadian study found that compared to married or cohabiting women, adverse birth outcomes such as stillbirth, infant mortality, and preterm birth among single women were significantly worse.[56] This study highlights that the social and material benefits accompanied by marital status or cohabitation may be protective against disease, as was observed in our study. Examining the hardships experienced by single mothers that may cause and exacerbate adverse pregnancy and neonatal outcomes can be useful in effectively targeting this higher risk group.

An interesting observation in this study was that women in the missing categories of both marital status and of the deprivation indices had significantly higher odds of preeclampsia

compared to the married group and the quintile 1 group, respectively. Those who were missing an index are likely those who were either missing a postal code, which was necessary for linking the deprivation index, or those who declined to put down information about their postal codes, or those whose postal codes did not have a match in the index, meaning they were not included in the Canadian Census. Women in this missing category are presumed to be those with unstable housing, or those with a disconnection with governmental bodies who collect administrative data. Efforts to gather more information about these groups, and to meaningfully engage and include them in health data collection, are warranted.

We used two ethnicity data sources to explore if different ethnic groups experience higher or lower frequency of preeclampsia compared to the general population. Using the previously-validated Chinese and South Asian name algorithm,[57,58] South Asians, and to a larger degree, Chinese women, had significantly reduced odds of preeclampsia. In addition to the validated name algorithm, we assessed occurrence of preeclampsia among South Asian, Chinese, and Filipino women, using previous country of residence. Compared to the general population, women from China had statistically significant 63% reduced odds (aOR 0.37, 95% CI 0.27-0.51), while women of Filipino origin had 52% increased odds (aOR 1.52, 95% CI 1.35-1.72) of preeclampsia, independently of other risk factors. Looking at the ORs yielded from the different models, it is noteworthy that the odds of preeclampsia decreased as the model adjusted for more risk factors. In the case of Filipino ethnicity, the age- and parity-adjusted ORs decreased by 7% when further adjusted for diabetes and chronic hypertension and CVD. This decrease suggests that while some of the burden of preeclampsia among Filipino women could be accounted for by these prior conditions, the rest of the burden manifests through different pathways.

Both the name algorithm and the previous country method were consistent with other ethnicity studies that showed similar association between Chinese and Filipino origins and preeclampsia.[15,59,60] Particularly, in the United States, Gong et al. found that women of Chinese and Filipino ethnicities had significantly reduced and increased odds, respectively, compared to non-Hispanic Whites.[15] This study also reported different preeclampsia odds within the South Central Asian group. Namely, women from India, Bangladesh, Pakistan had higher odds, while women from Afghanistan and Iran did not have different odds, compared to non-Hispanic White women. Conversely, we found that South Asians had 21% decreased odds (aOR 0.79, 95% CI 0.67-0.92) compared to the general population. These different results are difficult to interpret

because of methodological heterogeneity; whereas the aforementioned U.S. study had a specific ethnic comparison group (non-Hispanic White) which was based on self-report on birth records, our study used 'general population' as an amalgamation of Canadian-born Alberta citizens, based on surname algorithms.

Immigrants in our cohort also had decreased odds of preeclampsia compared to the general population. Several studies looking at immigrant status showed similar results,[61-63] including a systematic review and meta-analysis that reported that immigrant women have 0.74 (95% CI: 0.67-0.82) times the odds of pregnancy-related hypertensive disorders compared to non-immigrant women. The paradox of a traditionally lower social status group such as immigrants having lower disease could potentially be explained by the 'healthy immigrant effect,'[64] which posits that immigrants have a better health status when arriving to their destination country as compared to the native population. Research in Canada shows this is particularly true for chronic diseases such as cardiac disease and diabetes, which are important risk factors for preeclampsia.[64] Conceivably, women who immigrated to Canada would have lower prevalence of these risk factors, and thus although immigrants might experience social stress as new arrivals, these might be mitigated by their lower baseline risk set.

Our study found that women living in areas of lower material deprivation quintiles had higher odds of preeclampsia, with the largest association observed among women in quintile 4, as well as among women in the "missing" category. Other studies looking at SES levels and preeclampsia have shown that decreasing levels of neighbourhood-level wealth are associated with increasing levels of incidence.[23,59,65-68] In fact, SES has been a robust indicator of health inequalities not only in perinatal health, but also in CVD research. In our population, although quintiles 2-5 did have higher odds of preeclampsia compared to quintile 1, a clear dose-response relationship was not observed, with the lowest socioeconomic quintile (Q5) having lower odds of preeclampsia than the preceding quintile. This might be due to methodological limitations. The Canadian Deprivation Index assigns deprivation indices across regions by quintiles, meaning ordering the population into segments of 20% according to several different deprivation factors. However, 5.3% of our cohort was missing a deprivation index. This group likely represents the most vulnerable sector of society, and would have perhaps been captured in quintile 5, were they to be categorized in the index.

Of note, it is possible that the attenuated odds across the quintiles was observed not because lower SES does not have a bigger impact on preeclampsia, but because the reference group has higher rates of the disease. It is known that preeclampsia is more likely to occur in pregnancies conceived through in-vitro fertilization (IVF).[69,70] Considering that the costs for this fertility treatment goes above and beyond insurance coverage, IVF is thus more accessible for higher-income families. Because of this probable higher usage of IVF treatment in the reference group, the odds in the lower SES groups might be underestimated, biasing the OR towards the null.

Women with preeclampsia had greater odds of all adverse obstetrical and neonatal outcomes, including Casearian section, induction, preterm, SGA, and NICU stay compared to women with no preeclampsia, except having an LGA baby. Within the preeclampsia sub-cohort, we found no significant differences in any of the adverse maternal and neonatal outcomes between lower and higher SES groups. This might suggest that in Canada, once a woman has been diagnosed with preeclampsia during her pregnancy, and regardless of material deprivation status, she is likely to receive equitable clinical care thus mitigating the effects of the disease.

Strengths

To our knowledge, this is the first Canadian study to assess multiple SDOH and preeclampsia. A strength of this study is its use of a large (>400,000) population-based cohort data combining both clinical and social characteristics, which minimizes selection bias that may occur in hospital-based studies. Our assessment of several different social determinants in this population provides a holistic investigation from numerous perspectives of socioeconomic inequality and disease disparity, including geographical, social, and material deprivation. By using metropolitan influence to define rurality, this indicator is robustly and operationally defined as degree of rural isolation as well as access to major urban centers. This strengthens the validity of our 'rural' exposure construct. Our decision to assess associations between SDOH and preeclampsia using two models, one adjusting only for age and parity, and the other further adjusting for pre-existing disease, contributes to our understanding of possible mechanisms to explore in future research.

Limitations

A limitation in our study was the possibility of residual confounding. Data such as maternal BMI, often a pertinent risk factor of preeclampsia, was not available in the datasets, and the results do not take these data into account. As well, our study used ecological measures from the Canadian

Deprivation Index for SES. Postal codes may have been assigned multiple geographic areas according to the PCCF, and so some misclassification of rural and urban areas may have occurred, although it is not likely that geographic areas differed enough so as to be assigned a different classification. Despite the possibility that area-based measures underestimate inequality due to their imprecise nature, these are still considered to be valid in representing socioeconomic inequalities,[71] and indeed provide important information about relative disadvantage.[72]

Defining ethnicity based on last name algorithms connotes the possibility that some women who have changed their last names upon marriage could have been misclassified. Notably, people of South Asian and Chinese background are reported to be the least likely ethnic minority to be married to a partner outside of their ethnicity, thus lessening the likelihood that ethnic misclassification occurred in our study.[73] Additionally, using a second methodology, that of previous country, to define ethnicity, further corroborates the algorithm's findings, at least in the direction of association with preeclampsia. Another possibility of misclassification in our cohort study was that marital status was defined as married versus not married, though there could have been misclassification in the case of common law marriages, where a couple lives together but is never legally married. In Alberta, 16.8% of people living in a couple in 2016 were living in common law, and not legally married,[74] making it possible that some misclassification may have occurred.

A future opportunity in biopsychosocial research in the field of preeclampsia would be to combine epidemiological data with emerging knowledge about different subtypes of preeclampsia. Preeclampsia has two known distinct onset-based subtypes: early-onset and late-onset. The former is associated with worse maternal and fetal adverse outcomes, and is more commonly associated with long-term maternal CVD and renal disease risk.[75] Our study did not distinguish between the two subtypes, and so it was not possible to assess if different severities and types of disease were differently distributed across the SDOH. Lisonkova and her colleagues assessed risk factors, including education, race, and marital status, of late-onset and early-onset preeclampsia, compared to ongoing pregnancies of similar gestation. They found that women of Black race were significantly more likely to have early-onset compared to late-onset preeclampsia.[53] Future epidemiological studies should assess whether subtypes of preeclampsia are differentially associated with certain social or economic statuses, for improved risk stratification.

An important additional limitation is that this study did not evaluate preeclampsia among important minorities in Canada, namely Aboriginal populations, an important minority in Alberta, as well as Black populations. Given that both of these groups had significantly elevated odds of preeclampsia in the systematic review and meta-analysis, it is important to quantify these minorities' risks and identify any disparities that may exist. Currently, there is no administrative database in Canada that systematically provides racial or ethnic information. Incorporating this type of data into administrative cohorts can be an important opportunity to provide more targeted and efficient secondary prevention programs in prenatal health.

3.5 Conclusion

Our population-based study showed that socioeconomic health disparities impact the incidence and outcomes of preeclampsia in pregnancy. Women living in rural areas, unmarried women, and women of Filipino ethnicity had a higher risk of preeclampsia. Additionally, increased preeclampsia occurrence was observed among women with higher material deprivation. In contrast, women who immigrated to Canada, and women of Chinese and South Asian ethnicity had significantly lower odds of preeclampsia compared to the general population. Although medical services are offered to all Canadians, it is important to note that some socially and materially disadvantaged groups experience higher rates of disease. These findings support the emerging research linking the SDOH to obstetric and perinatal disease.

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CHAPTER 4: Summary of Findings and Conclusions

Social epidemiology asserts that disease is a product of several interacting factors, including not only individual risks, but also population-level sociocultural contexts. It is guided by the view that individual health is shaped by upstream factors, and it seeks to determine distributions of disease in a population according to socioeconomic stratifications. By looking at disease from this lens, important patterns valuable for public health strategies can emerge.[1] As discussed in Chapter 1 of this thesis, by using frameworks such as the Health Equity Measurement Framework (HEMF), epidemiologists can link social conditions to aberrant physiological changes that affect the body's stress response, which in turn lead to, modulate, or exacerbate, disease states.[2]

Preeclampsia is a disease of pregnancy with far-reaching cardiovascular (CVD), metabolic, and systemic sequelae on both the mother and child. Although the etiology of this disease is unknown, the placenta, an organ responsible for maternal-fetal nutrient and waste exchange, is thought to be central to disease development.[3] By applying the HEMF as well as an evidence-based hypothesis drawing on how social adversity affects the placenta, it is suggested that social and economic deprivation, including social stress stemming from factors such as racism, lack of access to resources, and poor living conditions, translate into insidious changes in the mother, the placenta, and the fetus, which in turn can lead to disease.[2,4]

This thesis evaluated the relationship between social determinants of health (SDOH) and preeclampsia. The first objective sought to synthesize the existing literature on this question in the form of a sysematic review and meta-analysis. The second objective used a large retrospective Pregnancy Birth Cohort study in Alberta, Canada, to determine the associations between immigrant status, marital status, rural residence, ethnicity, and social and economic deprivation, and preeclampsia.

4.1 Summary of Main Findings

4.1.1 Systematic Review and Meta-Analysis

The systematic review and meta-analysis included 52 studies evaluating the relationship between SDOH and preeclampsia. Pooled analyses were completed for sufficiently homogeneous studies according to Campbell and Cochrane Equity Methods Group guidelines.[5] Namely, Black race, Hispanic ethnicity, Native American ethnicity, education, and socioeconomic status (SES)

yielded pooled estimates, while other associations were evaluated in narrative form. Overall, African-American race, Native-American ethnicity, lower level of education, low SES, and unmarried status, had statistically significant and positive associations with preeclampsia. Of note, although different subgroups yielded variations in strength of association, Black race showed consistent and strong associations with preeclampsia, regardless of subgroup analysis, with the highest odds ratio (OR) being 1.67 (95% CI 1.64, 1.71) for the New York subgroup. Paucity of information was noted for rural residency status, specific Asian ethnicities, and employment status.

4.1.2 Alberta Pregnancy Birth Cohort Study

The retrospective Alberta Pregnancy Birth Cohort Study in this thesis included more than 400,000 singleton pregnancies, and used linked health and administrative data to decipher the relationship between key SDOH and preeclampsia. Overall, it was found that women living in rural areas, unmarried women, and women of Filipino ethnicity had a higher incidence of preeclampsia, but that women who had immigrated to Canada, and Chinese and South Asian women had decreased incidence of preeclampsia, compared to the general population. Unexpectedly, women in the lowest material deprivation group (i.e., quintile 5), although having higher odds of preeclampsia compared to the most well-off quintile 1, failed to show higher odds compared to quintile 4. This observation discourages the likelihood of a dose-response relationship between SES and disease in our cohort. Another key observation in this study was that the groups with the strongest associations with preeclampsia were ones where no data was available, namely ones with unknown marital status and unknown social and material deprivation quintile. These groups are thought to be highly marginalized groups such as women with no fixed postal code, institutionalized persons, and Indigenous groups.

4.2 Opportunities for Further Research

This thesis focused on associations between key SDOH and preeclampsia. We did not aim to evaluate hypotheses regarding the pathways through which these relationships occur, whether through the effects of general lack of access to healthcare resources, specific prenatal care access, and prevalence of key underlying risk factors among different socioeconomic stratifications that may predispose certain groups to preeclampsia. Future research is needed to clarify the pathways leading from low SES and adverse social situations, to the development of this disease of pregnancy.

Further, this thesis evaluated preeclampsia as operationalized by a wide variety of definitions. Although culminating in similar clinical manifestations (hypertension and proteinuria or other signs of end-organ damage), it has been posited that the mechanisms underlying preeclampsia are quite divergent, and that preeclampsia is actually a syndrome comprised of different disease pathways leading to a similar presentation.[6] Consequently, it could be that some subtypes of preeclampsia have stronger associations with a woman's social situation, than others. Future epidemiological research on SDOH should differentiate between different subtypes of preeclampsia (for example, early versus late-onset types) in order to further elucidate the relationships that exist between social conditions and preeclampsia.

4.3 Conclusions

This thesis explored, through a systematic review and meta-analysis (Chapter 2), as well as a population-based retrospective Alberta cohort study (Chapter 3), how the SDOH are associated with preeclampsia. The main findings of Chapter 2 suggest that several factors, including race/ethnicity, low SES, and marital status, are positively associated, while other factors such as immigrant status, are negatively associated, with preeclampsia. Chapter 3 further confirmed that low SES, and to a higher degree marital status as well as rural residence, were positively associated, while immigrant status, Chinese ethnicity, and South Asian ethnicity, were negatively associated, with preeclampsia. This research provides a population-level, biopsychosocial lens that complements biomedical preeclampsia research. Elucidating how social stress and inequality can affect women and children in pregnancy can be an important entry point for better understanding the health of communities.

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APPENDICES

Appendix 1: MOOSE Checklist

MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition	Yes	10
Hypothesis statement	Yes	11
Description of Study Outcome(s)	Yes	12
Type of exposure or intervention used	Yes	12
Type of study design used	Yes	12
Study population	Yes	13
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)	Yes	11
Search strategy, including time period included in the synthesis and keywords	Yes	11
Effort to include all available studies, including contact with authors	Yes	13
Databases and registries searched	Yes	11
Search software used, name and version, including special features used (eg, explosion)	Yes	12
Use of hand searching (eg, reference lists of obtained articles)	No	n/a
List of citations located and those excluded, including justification	Yes	Appendix 5
Method for addressing articles published in languages other than English	Yes	12
Method of handling abstracts and unpublished studies	Yes	12
Description of any contact with authors	Yes	4
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	12
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	12 (PROGRES
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	13,14 (multip
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate	Yes	13 (quality a

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	13
Assessment of heterogeneity	Yes	14
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	14
Provision of appropriate tables and graphics	Yes	13
Reporting of Results		
Table giving descriptive information for each study included	Yes	17-25
Results of sensitivity testing (eg, subgroup analysis)	Yes	14
Indication of statistical uncertainty of findings	Yes	14
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)	No	n/a
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	47
Assessment of quality of included studies	Yes	26
Reporting of Conclusions		
Consideration of alternative explanations for observed results	Yes	44
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	44-46
Guidelines for future research	Yes	47
Disclosure of funding source	Yes	47

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Appendix 2: Medical Subject and Heading Terms Used in the Systematic Review and Meta-Analysis

MESH term searches for Medline

1. (preeclamp* or pre-eclamp* or eclamp*).mp.
2. exp Pre-Eclampsia/
3. exp Eclampsia/
4. 1 or 2 or 3
5. (Socioeconomic status or socioeconomic circumst* or socioeconomic factor* or socioeconomic gradient* or socioeconomic health* or socioeconomic position*).mp.
6. exp "Social Determinants of Health"/
7. determinant* of health.mp.
8. exp *Socioeconomic Factors/
9. exp *Homeless Persons/ or exp *"Transients and Migrants"/ or ((vulnerable or migrant or transient*) adj2 (people or person* or individual* or population* or worker* or women or woman)).ti. or (street adj2 (people or person* or individual* or population* or women or woman)).ti. or ("lack of housing" or substandard housing or unstably housed or underhoused or under housed or squatter* or homeless* or vagrant* or indigent).mp. or (marginal* adj2 (population* or people* or group* or hous*)).ti.
10. immigra*.ti,ab,kf.
11. exp *"Emigration and Immigration"/
12. exp *Poverty/ or (poverty or low income).ti,ab,kf.
13. ethnic*.ti. or ethnic*.ab. /freq=2
14. social inequalit*.ti,ab,kf.
15. (social status or unemploy* or underemploy* or under employ* or working conditions or working poor).ti,ab,kf.
16. exp *Religion/ or (anthroposoph* or pastoral care or spiritual* or faith or faiths or theolog* or religion* or religious or meaningfulness or evangelical* or belief system* or Anabaptist* or Anglican* or Apostolic* or Bahai* or Baptist* or Buddhis* or Catholic* or Confucianism or Hindu* or Islam* or Jehovah's Witness* or Judiaism* or Latterday Saint* or Lutheran* or Mennonite* or Hutterite* or Mormon* or Muslim or Mysticism* or Pentacostal* or Presbyterian* or Protestant* or Seventh Day Adventist* or Shinto* or Sikh* or God or monotheis*).mp. or (Jewish or Christian* or church*).ti,ab.
17. exp *educational status/ or educational status.ti,ab,kf.
18. exp *Social Capital/
19. *vulnerable populations/
20. Working Poor/
21. (education* adj (status or attainment or achievement*)).ti,ab,kf.
22. (illitera* or literacy).ti. or (illitera* or literacy).ab. /freq=2
23. refugee*.ti,kf. or refugee*.ab. /freq=2

24. (language* or nonEnglish or non-English or language minority).ti.

25. (non-English or nonEnglish).ab.

26. language*.ab. /freq=2

27. (remote adj2 (area* or region* or population*)).ti,ab,kf. or (rural or urban).ti. or (place of residence or area of residence).ti,ab,kf.

28. race.ti. or race.ab. /freq=2

29. or/5-28

30. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal*.ti,ab. or prospective*.ti,ab. or retrospective*.ti,ab.

31. Epidemiologic Studies/

32. Incidence/ or exp Prevalence/ or (incidence or prevalence).ti,ab,kf.

33. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.

34. 30 or 31 or 32 or 33

35. 4 and 29 and 34

MESH term searches for EMBASE

1. (preeclamp* or pre-eclamp* or eclamp*).mp.

2. exp preeclampsia/

3. exp eclampsia/

4. 1 or 2 or 3

5. (Socioeconomic status or socioeconomic circumst* or socioeconomic factor* or socioeconomic gradient* or socioeconomic health* or socioeconomic position*).mp.

6. exp "social determinants of health"/

7. determinant* of health.mp.

8. exp *socioeconomics/

9. exp *homeless person/

10. exp *immigrant/

11. ((vulnerable or migrant or transient*) adj2 (people or person* or individual* or population* or worker* or women or woman)).ti.

12. (street adj2 (people or person* or individual* or population* or women or woman)).ti. or ("lack of housing" or substandard housing or unstably housed or underhoused or under housed or squatter* or homeless* or vagrant* or indigent).mp. or (marginal* adj2 (population* or people* or group* or hous*)).ti.

13. immigra*.ti,ab,kw.

14. exp *poverty/ or (poverty or low income).ti,ab,kw.

15. ethnic*.ti. or ethnic*.ab. /freq=2

16. social inequalit*.ti,ab,kw.

17. (social status or unemploy* or underemploy* or under employ* or working conditions or working poor).ti,ab,kw.

18. exp *religion/

19. (anthroposoph* or pastoral care or spiritual* or faith or faiths or theolog* or religion* or religious or meaningfulness or evangelical* or belief system* or Anabaptist* or Anglican* or Apostolic* or Bahai* or Baptist* or Buddhis* or Catholic* or Confucianism or Hindu* or Islam* or Jehovah's Witness* or Judiaism* or Latterday Saint* or Lutheran* or Mennonite* or Hutterite* or Mormon* or Muslim or Mysticism* or Pentacostal* or Presbyterian* or Protestant* or Seventh Day Adventist* or Shinto* or Sikh* or God or monotheis*).mp. or (Jewish or Christian* or church*).ti,ab.

20. exp *social capital/

21. exp vulnerable population/

22. exp *vulnerable population/

23. exp *educational status/ or educational status.ti,ab,kw.

24. exp working poor/

25. (education* adj (status or attainment or achievement*)).ti,ab,kw.

26. (illitera* or literacy).ti. or (illitera* or literacy).ab. /freq=2

27. refugee*.ti,kw. or refugee*.ab. /freq=2

28. (language* or nonEnglish or non-English or language minority).ti.

29. (non-English or nonEnglish).ab.

30. language*.ab. /freq=2

31. (remote adj2 (area* or region* or population*)).ti,ab,kw. or (rural or urban).ti. or (place of residence or area of residence).ti,ab,kw.

32. race.ti. or race.ab. /freq=2

33. or/5-32

34. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal*.ti,ab. or prospective*.ti,ab. or retrospective*.ti,ab.

35. exp epidemiology/

36. exp incidence/ or exp prevalence/ or (incidence or prevalence).ti,ab,kw.

37. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.

38. 34 or 35 or 36 or 37

39. 4 and 33 and 38

MESH term searches for Pubmed

(((((preeclamp*) OR pre-eclamp*) OR eclamp*)) AND ((((((((((((((((((((“social determinants of health”) OR “socioeconomic factors”) OR income) OR immigra*) OR poverty) OR religio*) OR educat*) OR social capital) OR social isolation) OR vulnerable population*) OR working poor) OR refugee) OR rural) OR “rural health services”) OR remote) OR “rural health”) OR “rural

population") OR "suburban population") OR "urban population") OR ethnic*) OR social inequalit*) AND ((((((("Case-Control Studies"[Mesh:noexp] OR "retrospective studies"[mesh:noexp] OR "Control Groups"[Mesh:noexp] OR (case[TIAB] AND control[TIAB]) OR (cases[TIAB] AND controls[TIAB]) OR (cases[TIAB] AND controlled[TIAB]) OR (case[TIAB] AND comparison*[TIAB]) OR (cases[TIAB] AND comparison*[TIAB]) OR "control group"[TIAB] OR "control groups"[TIAB])))) OR ((Incidence[mesh:noexp] OR incidence[tiab])))) OR "Epidemiologic Studies"[Mesh:noexp]) OR (cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]))

MESH term searches for CINAHL

S22	S20 AND S21	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	Display
S21	S14 OR S15 OR S16 OR S17 OR S18 OR S19	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	Display
S20	S12 OR S13	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	Display
S19	"low income" OR "household income" OR "income level" OR "family income" OR poverty OR "social inequalit*" OR	Limiters - Full Text Expanders -	Interface - EBSCOhost Research	Display

	"vulnerable population*" OR "working poor" OR "social isolation"	Apply equivalent subjects Search modes - Find all my search terms	Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	
S18	(MH "Occupations and Professions+") OR (MH "Education+") OR (MH "Social Capital")	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	Display
S17	(MH "Immigrants+") OR (MH "Emigration and Immigration") OR (MH "Ethnic Groups+") OR (MH "Race Factors") OR (MH "Religion and Religions+") OR (MH "Culture+") OR (MH "Refugees")	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	Display
S16	remote OR "remote area" OR "remote region" OR "remote population"	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	Display
S15	(MH "Rural Population") OR (MH "Rural Health Services") OR (MH "Rural Health Centers") OR (MH "Urban Areas") OR (MH "Urban Population") OR (MH "Urban Health Services") OR (MH "Urban Health") OR (MH "Hospitals, Urban")	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	Display

S14	(MH "Social Determinants of Health") OR (MH "Socioeconomic Factors+") OR (MH "Health Status Disparities")	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	Display
S13	preeclamp* OR eclamp* OR pre-eclamp*	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	Display
S12	(MH "Pre-Eclampsia+")	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	Display
S11	S9 AND S10	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	235
S10	S3 OR S4 OR S5 OR S6 OR S7 OR S8	Limiters - Full Text Expanders - Apply equivalent subjects Search modes	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database -	368,228

		- Find all my search terms	CINAHL Plus with Full Text	
S9	S1 OR S2	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	2,262
S8	"low income" OR "household income" OR "income level" OR "family income" OR poverty OR "social inequalit*" OR "vulnerable population*" OR "working poor" OR "social isolation"	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	24,060
S7	(MH "Occupations and Professions+") OR (MH "Education+") OR (MH "Social Capital")	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	272,196
S6	(MH "Immigrants+") OR (MH "Emigration and Immigration") OR (MH "Ethnic Groups+") OR (MH "Race Factors") OR (MH "Religion and Religions+") OR (MH "Culture+") OR (MH "Refugees")	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	17,597
S5	remote OR "remote area" OR "remote region" OR "remote population"	Limiters - Full Text Expanders - Apply equivalent	Interface - EBSCOhost Research Databases Search Screen -	4,961

		subjects Search modes - Find all my search terms	Basic Search Database - CINAHL Plus with Full Text	
S4	(MH "Rural Population") OR (MH "Rural Health Services") OR (MH "Rural Health Centers") OR (MH "Urban Areas") OR (MH "Urban Population") OR (MH "Urban Health Services") OR (MH "Urban Health") OR (MH "Hospitals, Urban")	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	16,431
S3	(MH "Social Determinants of Health") OR (MH "Socioeconomic Factors+") OR (MH "Health Status Disparities")	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	110,962
S2	preeclamp* OR eclamp* OR pre-eclamp*	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	2,210
S1	(MH "Pre-Eclampsia+")	Limiters - Full Text Expanders - Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL Plus with Full Text	1,502

MESH term searches for Sociological Abstracts

(pre-eclamp* OR preeclamp* OR eclamp*) AND (((((((social determinants of health) OR determinant* AND of health) OR socioeconomic factors) OR income) OR immigra*) OR poverty) OR ethnic*) OR social inequalit*)

Appendix 3: Full text inclusion/exclusion form

Full-Text Inclusion/Exclusion Form

Instructions:

- Retrieve and read the full text of each study. Determine if the papers included at the title and abstract phase meet each inclusion criteria. Each study must fulfill every criteria regarding study design, study population, exposure studied, and outcome reported. Otherwise, exclude the article and keep track of the reason(s) for exclusion.
- Highlight/flag useful information in the article that may be used for the data extraction in the next stage of the systematic review.

Reference ID:	Authors:	Reviewer initials:	Year of Publication:		
1. Study Design					
a) Primary research (exclude reviews, letters to the editor, editorials, etc.)			Yes	No	Unclear
b) Is study design one of the following? • Prospective cohort study • Retrospective cohort study • Cross sectional study			Yes	No	Unclear
2. Population					
a) Does the study address the question of SDOH effect on preeclampsia?			Yes	No	Unclear
3. Exposure					
a. Does the study address the question of SDOH effect on preeclampsia?			Yes	No	Unclear
b. Is the exposure one of the following SDOH? • place of residence • race/ethnicity/culture/language • occupation • gender/sex • religion • education • socioeconomic status • social capital • other personal characteristics such as parents' education, and disability			Yes	No	Unclear
c. Is there an acceptable comparison group (i.e. those without the exposure of interest?)			Yes	No	Unclear
4. Study Outcomes					
a. Preeclampsia or eclampsia incidence or prevalence is reported using numeric data (ex: OR, percentages, raw numbers, etc.)?					
b. Definition of preeclampsia does not include gestational hypertension or other hypertensive disorders of pregnancy?					

Appendix 4: Newcastle-Ottawa Quality Assessment Form

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community
   b) somewhat representative of the average _____ in the community
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records)
   b) structured interview
   c) written self report
   d) no description

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor)
   b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment
   b) record linkage
   c) self report
   d) no description

2) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost)
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CROSS SECTIONAL STUDIES

**This assessment scale was originally adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to perform a quality assessment of cross-sectional studies for the systematic review, "Are Healthcare Workers' Intentions to Vaccinate Related to their Knowledge, Beliefs and Attitudes? A Systematic Review", by Herzon R, Alvarez-Pasquin MJ, Diaz C, Del Barrio JL, Estrada JM, and Gil A.*

Selection: (maximum 5 stars)

1) Representativeness of the sample
   a) Truly representative of the average in the target population. * (all subjects or random sampling)
   b) Somewhat representative of the average in the target population. * (non-random sampling)
   c) Selected group of users.
   d) No description of the sampling strategy

2) Sample size
   a) Justified and satisfactory *
   b) Not justified

3) Non-respondents
   a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *
   b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
   c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor)
   a) Validated measurement tool. **
   b) Non-validated measurement tool, but the tool is available or described.*
   c) No description of the measurement tool.

Comparability (Max 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
   a) The study controls for the most important factor (select one). *
   b) The study control for any additional factor. *

Outcome (max. 3 stars)

1) Assessment of the outcome:
   a) Independent blind assessment. **
   b) Record linkage. **
   c) Self-report. *
   d) No description.

2) Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *
b) The statistical test is not appropriate, not described or incomplete.

SCORE: _____

Cohort studies

Good: 5-7

Fair: 3-4

Poor: <3

Cross Sectional studies

Good: 7-9

Fair: 4-6

Poor: <4

Appendix 5: List of References Excluded from the Systematic Review and Meta-Analysis, by Reason of Exclusion

Not primary research (9)

1. Lopez-Quesada E, Prada E. Immigration obstetrics in a regional hospital. gestational morbidity: Pathology of immigration-associated pregnancy. Ginecologia y Obstetricia Clinica 2005;6(1):8-10.
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Study design not acceptable (34)

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Study population is not pregnant women without preeclampsia (16)

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Study does not address SDOH relationship to PE (64)

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Duplicate (11)

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Appendix 6: Supplementary Figures

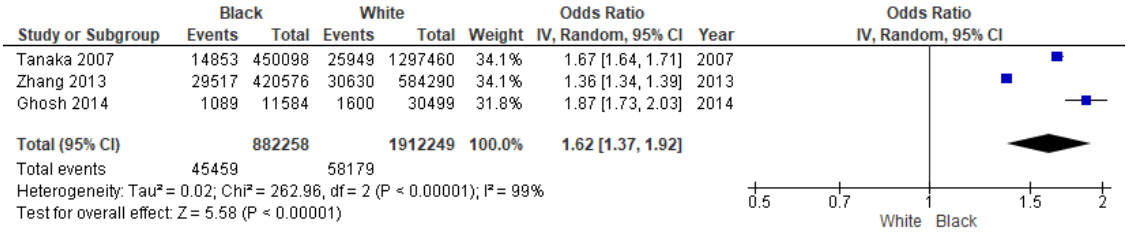
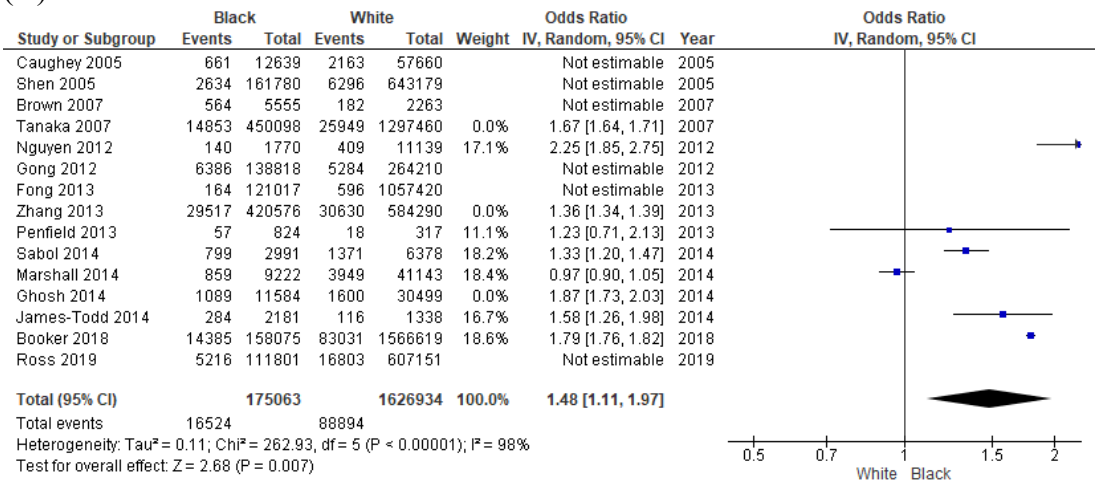


Figure S1: Black race assessed as a risk factor of preeclampsia in three retrospective U.S. cohort studies that defined preeclampsia as a combined variable including preeclampsia, eclampsia, and chronic hypertension superimposed by preeclampsia. The high heterogeneity limits any conclusions and is thus not presented in the main results of the systematic review.

(A)



(B)

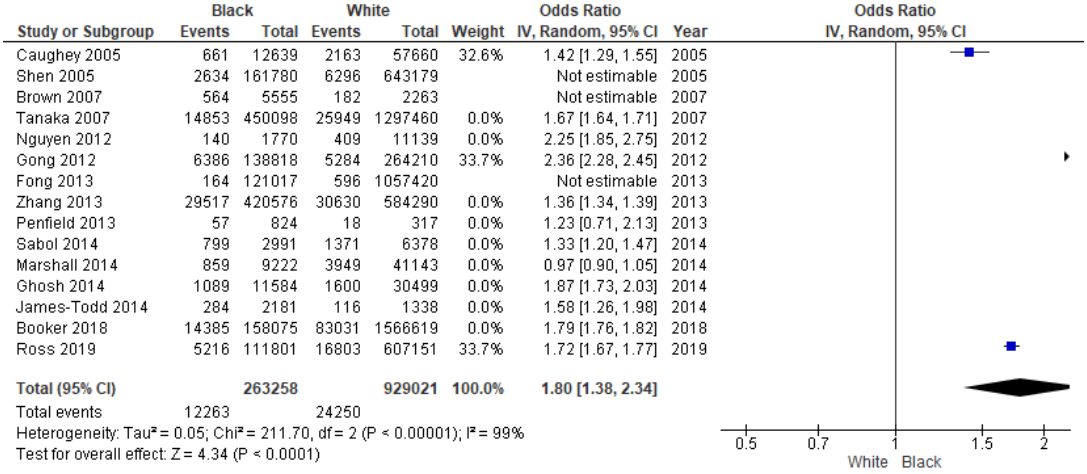
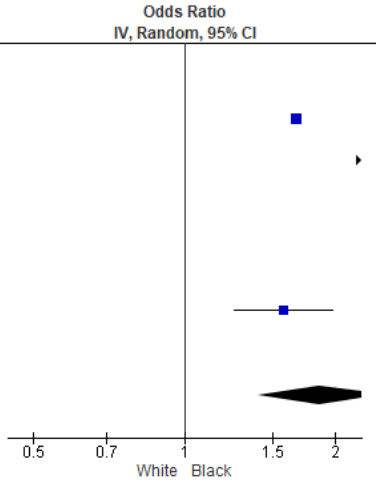


Figure S2: Black race assessed as a risk factor of preeclampsia in studies assessing high-risk **(A)** and low-risk **(B)** populations. The high heterogeneity limits any conclusions and is thus not presented in the main results of the systematic review.

(A)

Study or Subgroup	Black Events	Black Total	White Events	White Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Caughey 2005	661	12639	2163	57660	0.0%	1.42 [1.29, 1.55]	2005
Shen 2005	2634	161780	6296	643179		Not estimable	2005
Brown 2007	564	5555	182	2263		Not estimable	2007
Tanaka 2007	14853	450098	25949	1297460	35.6%	1.67 [1.64, 1.71]	2007
Nguyen 2012	140	1770	409	11139	0.0%	2.25 [1.85, 2.75]	2012
Gong 2012	6386	138818	5284	264210	35.5%	2.36 [2.28, 2.45]	2012
Fong 2013	164	121017	596	1057420		Not estimable	2013
Zhang 2013	29517	420576	30630	584290	0.0%	1.36 [1.34, 1.39]	2013
Penfield 2013	57	824	18	317	0.0%	1.23 [0.71, 2.13]	2013
Sabol 2014	799	2991	1371	6378	0.0%	1.33 [1.20, 1.47]	2014
Marshall 2014	859	9222	3949	41143	0.0%	0.97 [0.90, 1.05]	2014
Ghosh 2014	1089	11584	1600	30499	0.0%	1.87 [1.73, 2.03]	2014
James-Todd 2014	284	2181	116	1338	28.9%	1.58 [1.26, 1.98]	2014
Booker 2018	14385	158075	83031	1566619	0.0%	1.79 [1.76, 1.82]	2018
Ross 2019	5216	111801	16803	607151	0.0%	1.72 [1.67, 1.77]	2019
Total (95% CI)		**591097**		**1563008**	**100.0%**	**1.86 [1.40, 2.46]**	
Total events	21523		31349				

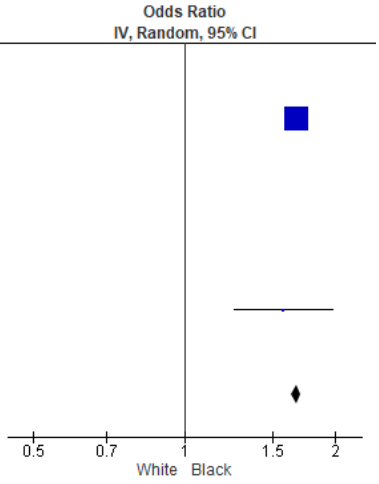
Heterogeneity: Tau² = 0.06; Chi² = 257.89, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 4.31 (P < 0.0001)



(B)

Study or Subgroup	Black Events	Black Total	White Events	White Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Caughey 2005	661	12639	2163	57660	0.0%	1.42 [1.29, 1.55]	2005
Shen 2005	2634	161780	6296	643179		Not estimable	2005
Brown 2007	564	5555	182	2263		Not estimable	2007
Tanaka 2007	14853	450098	25949	1297460	99.2%	1.67 [1.64, 1.71]	2007
Nguyen 2012	140	1770	409	11139	0.0%	2.25 [1.85, 2.75]	2012
Gong 2012	6386	138818	5284	264210	0.0%	2.36 [2.28, 2.45]	2012
Fong 2013	164	121017	596	1057420		Not estimable	2013
Zhang 2013	29517	420576	30630	584290	0.0%	1.36 [1.34, 1.39]	2013
Penfield 2013	57	824	18	317	0.0%	1.23 [0.71, 2.13]	2013
Sabol 2014	799	2991	1371	6378	0.0%	1.33 [1.20, 1.47]	2014
Marshall 2014	859	9222	3949	41143	0.0%	0.97 [0.90, 1.05]	2014
Ghosh 2014	1089	11584	1600	30499	0.0%	1.87 [1.73, 2.03]	2014
James-Todd 2014	284	2181	116	1338	0.8%	1.58 [1.26, 1.98]	2014
Booker 2018	14385	158075	83031	1566619	0.0%	1.79 [1.76, 1.82]	2018
Ross 2019	5216	111801	16803	607151	0.0%	1.72 [1.67, 1.77]	2019
Total (95% CI)		**452279**		**1298798**	**100.0%**	**1.67 [1.64, 1.71]**	
Total events	15137		26065				

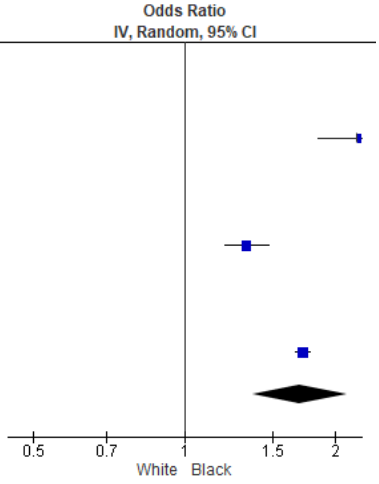
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 49.41 (P < 0.00001)



(C)

Study or Subgroup	Black Events	Black Total	White Events	White Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Caughey 2005	661	12639	2163	57660	0.0%	1.42 [1.29, 1.55]	2005
Shen 2005	2634	161780	6296	643179		Not estimable	2005
Brown 2007	564	5555	182	2263	0.0%	1.29 [1.08, 1.54]	2007
Tanaka 2007	14853	450098	25949	1297460	0.0%	1.67 [1.64, 1.71]	2007
Nguyen 2012	140	1770	409	11139	28.5%	2.25 [1.85, 2.75]	2012
Gong 2012	6386	138818	5284	264210	0.0%	2.36 [2.28, 2.45]	2012
Fong 2013	164	121017	596	1057420		Not estimable	2013
Zhang 2013	29517	420576	30630	584290	0.0%	1.36 [1.34, 1.39]	2013
Penfield 2013	57	824	18	317	0.0%	1.23 [0.71, 2.13]	2013
Sabol 2014	799	2991	1371	6378	34.5%	1.33 [1.20, 1.47]	2014
Marshall 2014	859	9222	3949	41143	0.0%	0.97 [0.90, 1.05]	2014
Ghosh 2014	1089	11584	1600	30499	0.0%	1.87 [1.73, 2.03]	2014
James-Todd 2014	284	2181	116	1338	0.0%	1.58 [1.26, 1.98]	2014
Booker 2018	14385	158075	83031	1566619	0.0%	1.79 [1.76, 1.82]	2018
Ross 2019	5216	111801	16803	607151	37.0%	1.72 [1.67, 1.77]	2019
Total (95% CI)		**116562**		**624668**	**100.0%**	**1.70 [1.37, 2.11]**	
Total events	6155		18583				

Heterogeneity: Tau² = 0.03; Chi² = 30.76, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 4.76 (P < 0.00001)



(D)

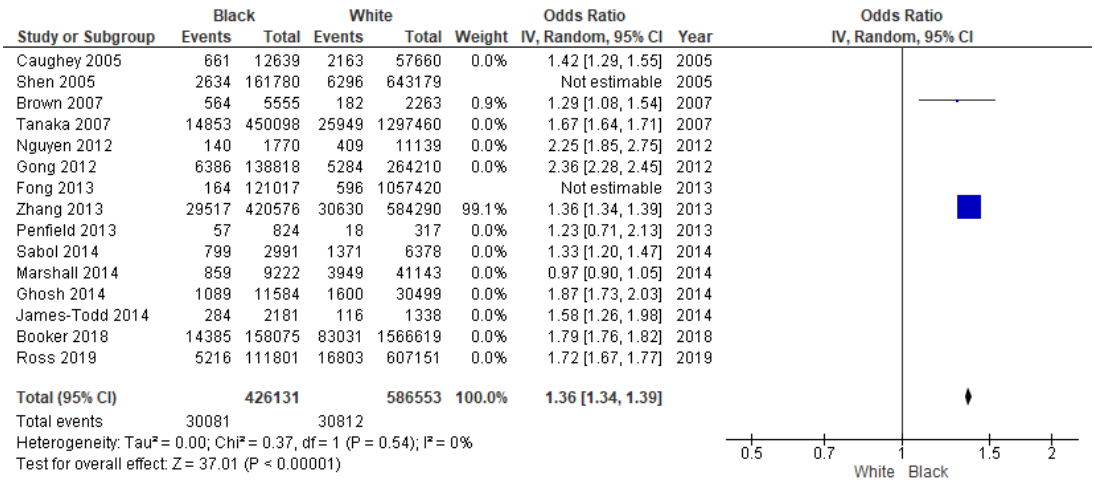
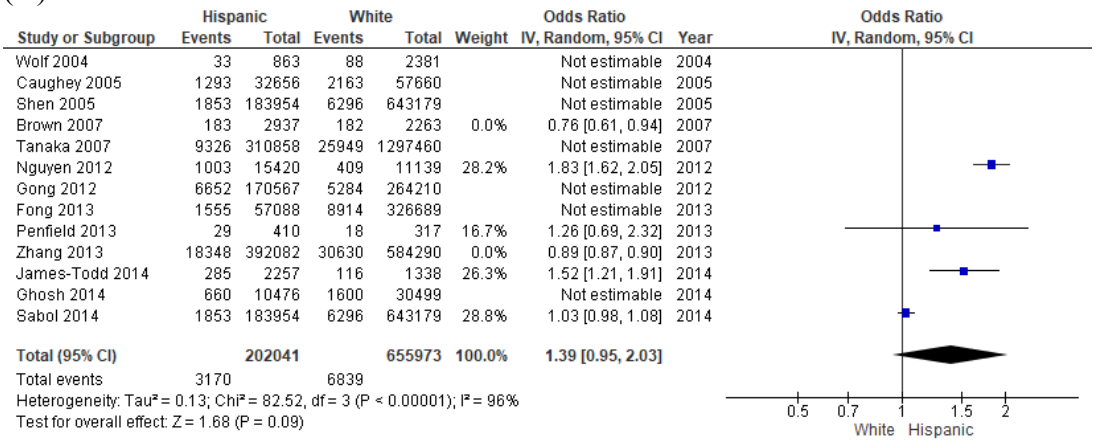


Figure S3: Black race assessed as a risk factor of preeclampsia in studies taking place in New York State **(A),** New York City **(B),** California **(C)**, and southern states **(D)**. The high heterogeneity of forest plots A and C limits any conclusions and these are thus not presented in the main results of the systematic review.

(A)



(B)

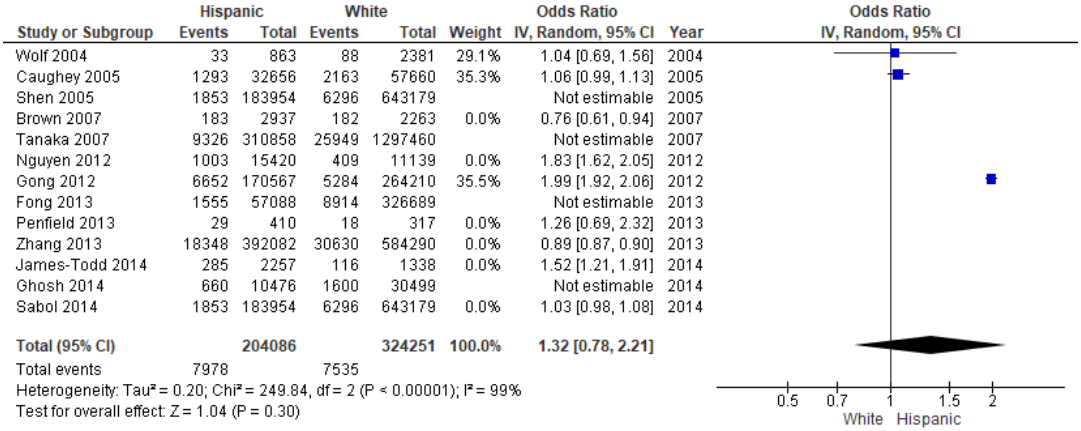
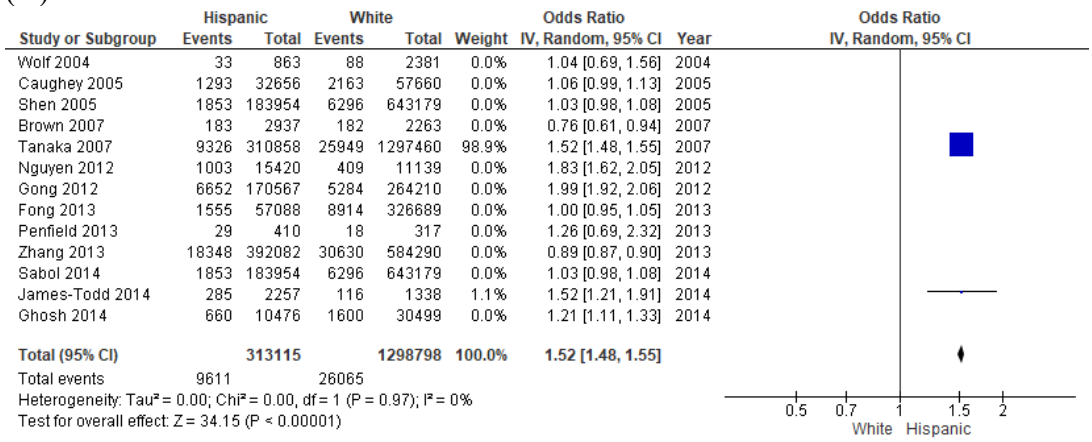
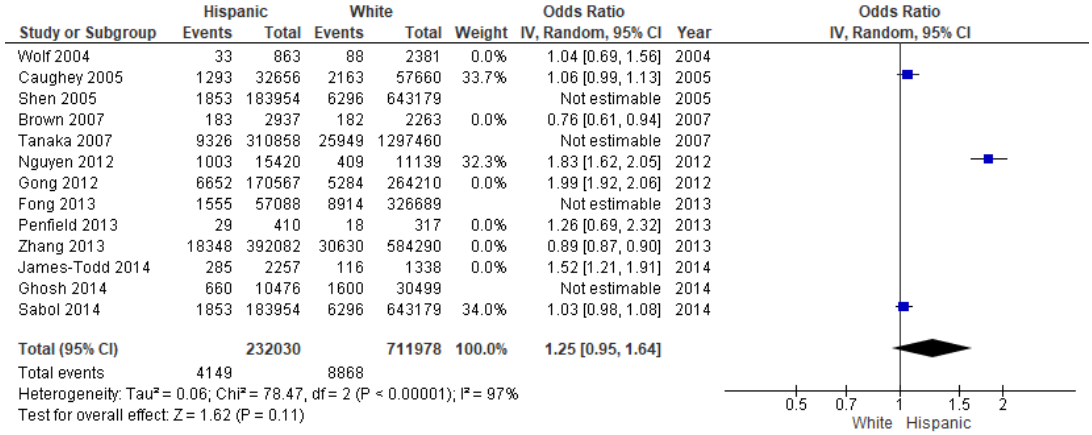


Figure S4: Hispanic ethnicity assessed as a risk factor of preeclampsia in studies assessing high-risk **(A)** and low-risk **(B)** populations. The high heterogeneity limits any conclusions and is thus not presented in the main results of the systematic review.

(A)



(B)



(C)

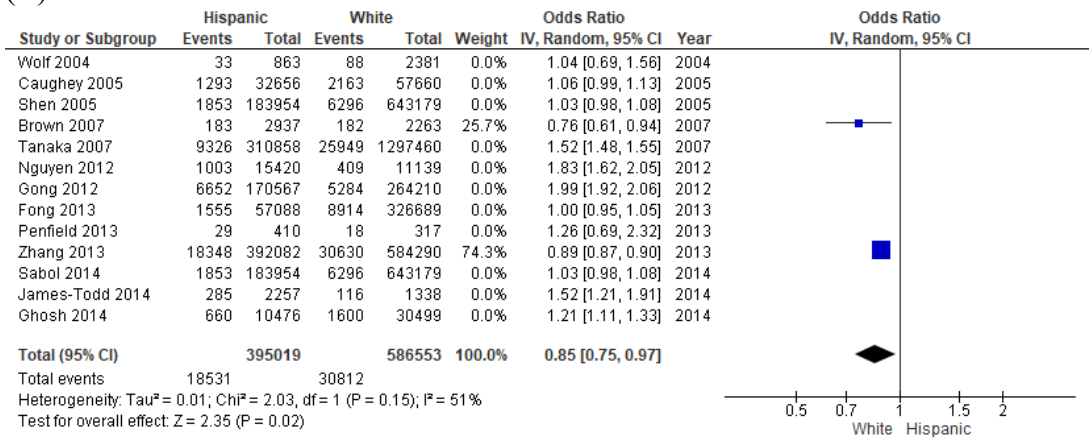


Figure S5: Hispanic ethnicity assessed as a risk factor of preeclampsia in studies situated in New York State **(A),** California **(B)** and southern states **(C)**. The high heterogeneity of the California

meta-analysis limits any conclusions and is thus not presented in the main results of the systematic review.

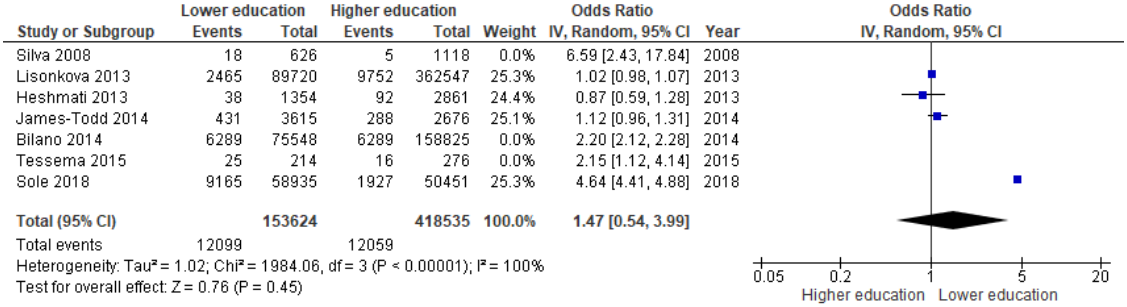


Figure S6: Education assessed as a risk factor of preeclampsia in the four retrospective cohort studies. The high heterogeneity limits any conclusions and is thus not presented in the main results of the systematic review.

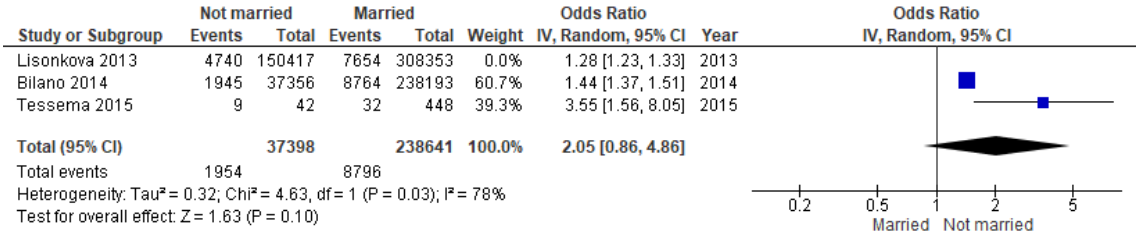


Figure S7: Marital status assessed as a risk factor of preeclampsia in two cross sectional studies. The high heterogeneity limits any conclusions and is thus not presented in the main results of the systematic review.

Appendix 7: Supplementary Table

Table S1: Material deprivation characteristics table (Preeclampsia only cohort)

	Material Deprivation Quintile						Total
	1 (high)	2	3	4	5 (low)	Missing	
Total	1403	1448	1360	1218	1034	434	6897
Age group							
12-19	21 (1.5)	47 (3.2)	57 (4.2)	63 (5.2)	132 (12.8)	23 (5.3)	343 (5.0)
20-30	636 (45.3)	734 (50.7)	728 (53.5)	669 (54.9)	549 (53.1)	227 (52.3)	3543 (51.4)
31-40	695 (49.5)	614 (42.4)	523 (38.5)	444 (36.5)	326 (31.5)	178 (41.0)	2780 (40.3)
41-54	51 (3.6)	53 (3.7)	52 (3.8)	42 (3.4)	27 (2.6)	6 (1.4)	231 (3.3)
Nulliparous	1149 (81.9)	1216 (84.0)	1128 (82.9)	988 (81.1)	814 (78.7)	331 (76.3)	5626 (81.6)
Previous cardiovascular disease or hypertension							
No	1382 (98.5)	1413 (97.6)	1333 (98.0)	1180 (96.9)	999 (96.6)	427 (98.4)	6734 (97.6)
CVD only	11 (0.8)	21 (1.5)	17 (1.3)	18 (1.5)	19 (1.8)	1 (0.2)	87 (1.3)
Both hypertension and CVD	10 (0.7)	14 (1.0)	10 (0.7)	20 (1.6)	16 (1.5)	6 (1.4)	76 (1.1)
Gestational Diabetes Mellitus	128 (9.1)	114 (7.9)	137 (10.1)	107 (8.8)	104 (10.1)	29 (6.7)	619 (9.0)
Previous Diabetes Mellitus	49 (3.5)	32 (2.2)	40 (2.9)	49 (4.0)	36 (3.5)	15 (3.5)	221 (3.2)
Rural residence	46 (3.3)	196 (13.5)	308 (22.6)	426 (35.0)	484 (46.8)	130 (30.0)	1590 (23.1)
Immigrant	277 (19.7)	206 (14.2)	223 (16.4)	212 (17.4)	168 (16.2)	66 (15.2)	1152 (16.7)
Married status							
Married	1095 (78.0)	999 (69.0)	893 (65.7)	739 (60.7)	536 (51.8)	273 (62.9)	4535 (65.8)
Not Married	304 (21.7)	443 (30.6)	465 (34.2)	472 (38.8)	491 (47.5)	159 (36.6)	2334 (33.8)

Missing	4 (0.3)	6 (0.4)	2 (0.1)	7 (0.6)	7 (0.7)	2 (0.5)	28 (0.4)
Ethnicity							
Chinese	42 (3.0)	30 (2.1)	15 (1.1)	16 (1.3)	10 (1.0)	9 (2.1)	122 (1.8)
General	1339 (95.4)	1398 (96.5)	1302 (95.7)	1168 (95.9)	983 (95.1)	411 (94.7)	6601 (95.7)
South Asian	22 (1.6)	20 (1.4)	43 (3.2)	34 (2.8)	41 (4.0)	14 (3.2)	174 (2.5)
Outcomes							
Caesarian section	754 (53.7)	795 (54.9)	747 (54.9)	648 (53.2)	531 (51.4)	232 (53.5)	3707 (53.7)
Induction	884 (63.0)	880 (60.8)	801 (58.9)	714 (58.6)	606 (58.6)	252 (58.1)	4137 (60.0)
Preterm	546 (38.9)	571 (39.4)	510 (37.5)	415 (34.1)	381 (36.8)	174 (40.1)	2597 (37.7)
SGA	312 (22.2)	307 (21.2)	278 (20.4)	253 (20.8)	205 (19.8)	83 (19.1)	1438 (20.8)
LGA	112 (8.0)	127 (8.8)	128 (9.4)	115 (9.4)	115 (11.1)	54 (12.4)	651 (9.4)
NICU stay	552 (39.3)	595 (41.1)	572 (42.1)	475 (39.0)	402 (38.9)	172 (39.6)	2768 (40.1)

Appendix 8: ICD-10 Codes

ICD-10 CODES	**ICD-9 CODES**	**DIAGNOSIS**
delhx_codeO11 delhx_codeO14 delhx_codeO15		Preeclampsia or eclampsia
O244, O248		Gestational Diabetes Mellitus
O240-O243, O245-O247, O249 E10-E14		Pre-existing diabetes mellitus
390-460	I, R000, R001, R570, R931, R943, T821, T817, T820, T825, T827, T828, Z450, Z452, T86200	Prior cardiovascular disease
401-405	I10-I15	Prior hypertension
PROCEDURE CODE		**PROCEDURE/OUTCOME**
5MD60		Delivery via Caesarian section
5AC30		Induction of labour