Person, Place and Context: The Interaction between the Social and Physical Environment on Adverse Pregnancy Outcomes in British Columbia

by

Anders Carl Erickson
B.Sc., University of Victoria, 2004
M.Sc., University of Northern British Columbia, 2009

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Supervisory Committee

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Abstract

This study was a population-based retrospective cohort of all singleton births in British Columbia for the years 2001 to 2006. The purpose of this dissertation is to examine how social and physical environment factors influence the risk of adverse pregnancy outcomes and whether they interact with each other or with maternal characteristics to modify disease risk. The main environmental factors examined include ambient particulate air pollution ($PM_{2.5}$), neighbourhood socioeconomic status (SES), neighbourhood immigrant density, neighbourhood level of post-secondary education level and the urban-rural context. Census dissemination areas (DAs) were used as the neighbourhood spatial unit. The data (N=242,472) was extracted from the BC Perinatal Data Registry (BCPDR) from Perinatal Services BC (PSBC). The main perinatal outcomes investigated include birth weight and indicators of fetal growth restriction such as small-for-gestational age (SGA), term low birth weight (tLBW), and intrauterine growth restriction (IUGR), preterm birth (PTB) and gestational age, gestational diabetes mellitus (GDM) and gestational hypertension (GH).

Collectively, this dissertation contributes to the perinatal epidemiological literature linking particulate air pollution and neighbourhood SES context to adverse pregnancy outcomes. Assumptions about the linear effect of $PM_{2.5}$ and smoking on birth weight are challenged showing that the effects are most pronounced between low and average exposures and that the magnitude of their effect is modified by neighbourhood and individual-level characteristics. These results suggest that focusing exclusively on individual risk factors may have limited success in improving outcomes without addressing the contextual influences at the neighbourhood-level. This dissertation therefore also contributes to the public health, sociological and community-urban development literature demonstrating that context and place matters.

Executive Summary

This study was a population-based retrospective cohort of all singleton births in British Columbia for the years 2001 to 2006. The purpose of this dissertation is to examine how social and physical environment factors influence the risk of adverse pregnancy outcomes and whether they interact with each other or with maternal characteristics to modify disease risk. The main environmental factors examined include ambient particulate air pollution ($PM_{2.5}$), neighbourhood socioeconomic status (SES), neighbourhood immigrant density, neighbourhood level of post-secondary education level and the urban-rural context. Census dissemination areas (DAs) were used as the neighbourhood spatial unit. The data (N=242,472) was extracted from the BC Perinatal Data Registry (BCPDR) from Perinatal Services BC (PSBC). The main perinatal outcomes investigated include birth weight and indicators of fetal growth restriction such as small-for-gestational age (SGA), term low birth weight (tLBW), and intrauterine growth restriction (IUGR), preterm birth (PTB) and gestational age, gestational diabetes mellitus (GDM) and gestational hypertension (GH).

The dissertation is comprised of 7 chapters. In Chapter 1, I review the shared pathoetiological effects of particulate air pollution and the social environment in contributing to adverse pregnancy outcomes, including the role of oxidative stress, inflammation and endocrine modification on fetal-placental development. Chapter 2 provides a background discussion on the methods and data used throughout the dissertation. This includes the hierarchical nature of the social environment and how multilevel and spatial statistical methods can be used to explore environmental health relationships. This leads into the four research chapters (Chapters 3 to 6) which show the existence of these relationships in an observational epidemiological setting. Finally, Chapter 7 provides the overall conclusions and recommendations. Additional maps, results and background information are provided as appendices. Research ethics board approval was granted by the University of Victoria (ethics protocol #: 11-043) and by the University of Alberta (study id: Pro00028662) with funding provided in part by the Canadian Institute of Health Research (CIHR) Operational Grant (protocol #: 200903-202069).

In the first research paper (Chapter 3), I assess the quantity of cigarettes smoked during pregnancy and the magnitude of adverse pregnancy outcomes followed by testing the association between the quantity of cigarettes smoked with other SES and behavioural risk factors that also influence pregnancy outcomes. The results show a significant dose-response increase in risk for SGA, tLBW and IUGR, and indicate that self-reports of heavy

smoking (≥ 10 cigarettes/day) early in pregnancy were associated with not having high school education: adjusted OR (95% CI) = 3.80 (3.41-4.25); being a single parent: 2.27 (2.14-2.42); indication drug or alcohol use: 7.65 (6.99-8.39) and 2.20 (1.88-2.59) respectively, and attending fewer than 4 prenatal care visits: 1.39 (1.23-1.58), and to be multiparous: 1.59 (1.51-1.68) compared to light, moderate and non-smokers combined. These results suggest that heavy smoking in pregnancy could be used as a marker for lifestyle risk factors that in combination with smoking influence birth outcomes. I use the number of cigarettes and this heavy smoking sub-population in the following two papers as a potential high risk group possibly more susceptible to $PM_{2.5}$ exposure.

The purpose of Chapter 4 was to determine the relationship between $PM_{2.5}$ exposure and continuous birth weight, and to test the potential modification by maternal risk factors and indicators of socioeconomic status. The results show a non-linear negative association of $PM_{2.5}$ and birth weight and that this relationship is modified by the neighbourhood context and maternal characteristics. Using random coefficient models, there is evidence that neighbourhood-level SES variables and $PM_{2.5}$ have both independent and interacting associations with birth weight which together account for 49% of the between-neighbourhood differences in birth weight. This suggests that certain sub-populations may be more or less vulnerable to even relatively low doses $PM_{2.5}$ exposure. I provide further analysis of the association between $PM_{2.5}$ and the other DA-level variables on measure of birth weight, including tLBW, SGA, IUGR as well as PTB in Appendix 3. The results show find consistent dose-response associations between $PM_{2.5}$ exposure and the measures of impaired fetal growth, but no association with PTB.

In Chapter 5 I focus on the interaction between maternal smoking and whether neighbourhood factors can either potentiate or buffer its negative effect on birth weight. Similar to $PM_{2.5}$, a significant negative and non-linear association was found between maternal smoking and birth weight which was highly variable between neighbourhoods and showed evidence of effect modification with neighbourhood-level factors. High DA-level SES had a strong positive association with birth weight but the effect was moderated with increased cigarettes/day. Conversely, heavy smokers showed the largest increases in birth weight with rising neighbourhood education levels. Increased levels of $PM_{2.5}$ and immigrant density were negatively associated with birth weight, but showed positive interactions with increased levels of smoking. Older maternal age and suspected drug or alcohol use both had

negative interactions with increased levels of maternal smoking. The results suggest that the social and environmental context matters in how smoking can affect birth weight.

In Chapter 6 I assess the association of $PM_{2.5}$ and SES-related neighbourhood factors on the risk of gestational hypertension (GH) and gestational diabetes mellitus (GDM). The results show a consistent dose-response association in the risk of GH and GDM with increasing levels of $PM_{2.5}$. Higher DA-level SES and education were associated with lower risks for both GH and GDM, while higher immigrant density and higher DA-mean BMI showed an increased risk. GDM showed considerable effect heterogeneity in urban areas where the interaction between $PM_{2.5}$ and SES greatly modified the risk of GDM. Furthermore, these associations are potentially more pronounced among mothers with larger pre-pregnancy BMI. The inclusion of the DA-level SES and $PM_{2.5}$ variables reduced a substantial proportion of the between-DA variability in the risk of GH and GDM; however, the was significant remaining unexplained random intercept variance which was shown to be, at least partially, spatially clustered at a local scale.

Collectively, this dissertation contributes to the perinatal epidemiological literature linking particulate air pollution and neighbourhood SES context to adverse birth outcomes. Assumptions about the linear effect of $PM_{2.5}$ and smoking on birth weight are challenged showing that the effects are most pronounced between low and average exposures and that the magnitude of their effect is modified by neighbourhood and individual-level characteristics. These results suggest that focusing exclusively on individual risk factors may have limited success in improving outcomes without addressing the contextual influences at the neighbourhood-level. This dissertation therefore also contributes to the public health, sociological and community-urban development literature demonstrating that context and place matters.

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List of Abbreviations

Acronym	Definition
11β-HSD2	11β-hydroxysteroid dehydrogenase type 2
AhR	Aryl Hydrocarbon Receptor
ACTH	Adrenocorticotropic Hormone
APO	Adverse Pregnancy/Perinatal Outcome
BC	British Columbia
BCPDR	British Columbia Perinatal Database Registry
BMI	Body Mass Index
CI	Confidence Interval
Cd	Cadmium
COX-2	Cyclo-oxygenase-2
CO, CO_2	Carbon Monoxide, Carbon Dioxide
CRA	Cumulative Risk Assessment
CRH	Corticotropin Releasing Hormone
CRP	C-reactive protein
CSD	Census Subdivision
CVD	Cardiovascular Disease
CYP	Cytochrome P450
DA	Dissemination Area
DPP	Defective Deep Placentation
ETS	Environmental Tobacco Smoke
EVT	Extravillious Trophoblast
FGR	Fetal Growth Restriction
GDM	Gestational Diabetes Mellitus
GH	Gestational Hypertension
GPx	Glutathione Peroxidase
GST	Glutathione-S-Transferase
HHC	Hyperhomocysteimia
HPA axis	Hypothalamus -Pituitary-Adrenal axis
ICC	Intra-class correlation
IUGR	Intra-Uterine Growth Restriction
I/R injury	Ischemic-reperfusion injury
LBW	Low Birth Weight
LDL	Low Density Lipoproteins
LHA	Local Health Area
LUR	Land Use Regression
MOR	Median Odds Ratio
MI	Multiple Imputation

NO, NO_2	Nitrogen Oxide/Dioxide
OR	Odds Ratio
PAH	Polycyclic Aromatic Hydrocarbons
PAP	Particulate Air Pollution
PCV	Proportional Change in Variance
PIH/PE	Pregnancy Induced Hypertension/Preeclampsia
PM	Particulate Matter
$PM_{2.5}$	Particulate Matter less than 2.5 microns in diameter
pPROM	(premature) Prelabour Rupture of Membranes
PSBC	Perinatal Services British Columbia
PTB	Preterm Birth
RI	Random Intercept
ROS	Reactive Oxygen Species
RS	Random Slope
sEng	soluble endoglin
sFlt	soluble fms-like tyrosine kinase
SES	Socio-economic Status
SESi	Socio-economic Status Index
SMR	Standardized Morbidity Rate
SNP	Single Nucleotide Polymorphism
SOD	Superoxide Dismutase
tLBW	Term Low Birth Weight
UFP	Ultrafine Particles
uNK (cells)	uterine natural killer

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First and foremost, I would like to acknowledge my supervisor and mentor over the past several years Dr. Laura Arbour. I wouldn't be here today without her support, guidance, patience, and encouragement. Her humility and whole-hearted approach to the important work that she does in academe, clinical and community settings is inspirational. Second, I'd like to thank Dr. Laurie Chan for his support over the past decade dating back to when I started my Masters in 2006. His mentorship over that time at UNBC taught me many lessons on how to be a graduate student and academic involved in community-level research. I'd like to thank Dr. Aleck Ostry for his on-point advice, insight, and the right dose of involvement when needed. A big thank you to former committee member Dr. Eleanor Setton for many things, from bringing me into CAREX to putting my name forward for various opportunities, Eleanor has been an enduring supporter and cheerleader. I'd like to acknowledge Dr. Scott Venners as a friend, supporter, and co-applicant on a CIHR grant that funded the majority of my PhD. I'd also like to acknowledge and thank Dr. Adrien Barnett for his mentorship over the past two years on several statistical issues. His fast and clear email responses were instrumental in moving my research forward. Thank you to colleagues Sarah, Beatrixe, Sorsha and Sirisha for all their help and friendly faces over these many years, as well as to Dr. Perry Hystad for the use of his air pollution data, advice and friendship. I'd like to acknowledge the staff at Perinatal Services BC for their support regarding data access and manuscript review. Finally, words cannot describe the unconditional support, friendship and love my life partner, best friend and wife Keeley Nixon provided throughout this journey. Whether killing me with kindness or just giving me space to wallow in my own despair, she is always there nourishing my heart, soul and stomach. Her copy-editing in the final push to get this dissertation in shape and off to my committee was invaluable, I love you so much.

Dedication

I would like to dedicate this dissertation to three people who inspired and encouraged me to pursue the study of medical and health geography. They include, Dr. Denise Cloutier, Dr. Patrick McLeod and the late Dr. Harry Foster. I was hired by Denise as a co-op student in the summer of 2002 to work for Patrick, a medical geneticist with a keen interest in disease mapping, in the Medical Genetics Clinic at Victoria General Hospital. Patrick's plucky enthusiasm and ability to communicate complex disease mechanisms and Denise's compassionate and feminist teachings of the social determinants of health got me hooked on medical sciences and epidemiology. I would continue to work and volunteer part-time for Patrick for the next two years, enrolling in the geography honours program with him and Denise as my co-supervisors. It was during this transition to health geography and enrollment into the honour program that I was introduced to Dr. Foster. His passion for the underlying environmental causations of various diseases, most notably selenium and other micronutrient deficiencies, sparked my interest the environmental links to health and disease. Coincidently, it was while working for Patrick that I met my current supervisor Dr. Laura Arbour who many years later introduced me to Dr. Laurie Chan which brought me back into academe for my Masters at UNBC and initiated this whole journey. Everything goes full-circle, and so this is why I dedicate this work of study to those three individuals.

Chapter 1: The Shared Pathoetiological Effects of Particulate Air Pollution and the Social Environment on Fetal-Placental Development

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Abstract

Exposure to particulate air pollution and socioeconomic risk factors are shown to be independently associated with adverse pregnancy outcomes; however, their confounding relationship is an epidemiological challenge that requires understanding of their shared etiologic pathways affecting fetal-placental development. The purpose of this paper is to explore the etiological mechanisms associated with exposure to particulate air pollution in contributing to adverse pregnancy outcomes and how these mechanisms intersect with those related to socioeconomic status. Here we review the role of oxidative stress, inflammation and endocrine modification in the pathoeitology of deficient deep placentation and detail how the physical and social environments can act alone and collectively to mediate the established pathology linked to a spectrum of adverse pregnancy outcomes. We review the experimental and epidemiological literature showing that diet/nutrition, smoking and psychosocial stress share similar pathways with that of particulate air pollution exposure to potentially exasperate the negative effects of either insult alone. Therefore, socially-patterned risk factors often treated as nuisance parameters should be explored as potential effect modifiers that may operate at multiple levels of social geography. The degree to which deleterious exposures can be ameliorated or exacerbated via community-level social and environmental characteristics needs further exploration.

1.0 Introduction

Over the last decade, chronic exposure to ambient air pollution has become increasingly recognized as an important risk factor underlying adverse pregnancy outcomes (APOs) [1–9]. In parallel, the associations between socio-economic status (SES) and APOs are among the most robust findings in perinatal research [10–12], which persist even in settings with universal access to health care [13–16]. While interest in the intersection between health and the social environment is long standing [17–19], renewed attention has been propelled by two independent progressions in quantitative research. The first is the popularization of multilevel statistical models and the ability to separate the individual-level effects from those of their encompassing social and physical environments [20–26].

The second is the emerging research on the biological effects of psychosocial stress on health and its modification by environmental factors. There is now mounting evidence that stress can interact with chemical exposures to exacerbate the toxic effect and the physiological response to a greater extent than either insult (stress or chemical) acting alone [27–31]. Furthermore, the accumulation of low-level exposures to multiple chemicals via multiple sources and pathways show evidence of dose addition and synergism [32–34]. For example, synergism was observed between aqueous cigarette tar and other respirable particles (e.g. asbestos fibers, particulate matter, diesel exhaust) [35]. Recognition of these interactions have been incorporated into several conceptual models and study designs of cumulative risk of chemical and non-chemical exposures [36–39] with models recently developed to identify these potentially double-exposed populations [40,41]. Two complimentary reviews of these models have been recently published [42,43].

Although the causes of APOs are multifactorial, the placenta plays the main intermediary role between the mother's physical and social environment and the fetus, [44–50]. Importantly, a perturbed intrauterine environment inhibiting the fetal growth trajectory may also have long-term adult health implications as suggested by the developmental origins of disease hypothesis [51–53]. Therefore efforts to understand the underlying mechanisms of the physical and social environment that contribute to the disproportionate risk of APOs across the socio-economic spectrum is required in order to target preventative and restorative interventions. This review will examine how the shared pathoetiological effects of exposure to particulate air pollution and SES act on the fetal-placental unit leading to adverse pregnancy outcomes. This will be accomplished by building on conceptual pathway models of air pollution and SES etiologic mechanisms on APOs [54,55]. We review the role of the placenta in this context, describing its physiology and obstetrical pathologies followed by a description of particulate air pollution, and its toxicokinetics in relation to placentation and how it can lead to APOs. We highlight specific indicators of SES and their biological pathways that intersect with air pollution exposure and how this may contribute to increased susceptibility for APOs. Potential implications and interventions are summarized in the conclusion. Our aim is for this review to be a resource for researchers interested in environmental-perinatal epidemiology. Understanding how correlated social and environmental exposures at times overlap to produce potential synergistic and modifiable effects will help guide future research and intervention strategies with the aim to improve the overall health of the population [36–40].

2.0 Person, Place and Context: The Placental, Physical and Social Environments

2.1 The Placenta

The mammalian placenta is multifunctional and vital to fetal development. Formed from two genetically distinct organisms, it is multifunctional and vital to fetal development yet situated outside the fetal body with a limited life span. Notable characteristics unique to humans and the Great Apes include deep interstitial implantation and a highly invasive hemochorial phenotype thus allowing the direct interaction of maternal blood and fetal chorionic tissues [56]. Interestingly, this particular aspect of placental evolution has less to do with nutrient transfer efficiency than previously thought and more likely implicates the highly regulated maternal-fetal immunological relationship [57–59].

The first trimester is a critical period in pregnancy involving implantation and initial placentation, two events highly susceptible to disturbance (see endnote 1). The "Great Obstetrical Syndromes" [60] such as early/recurrent miscarriage, pregnancy induced hypertension and preeclampsia (PIH/PE), fetal growth restriction (FGR), placental abruption, pre-labour rupture of the fetal membranes (PROM) and spontaneous preterm labour may share common etiological mechanisms arising from defective deep placentation (DDP)[61,62]. Together, these conditions may complicate between 17 to 29% of all pregnancies [63], and are for the purpose of this review referred to collectively as APOs. Furthermore, these conditions may lead to epigenetic programming of adult disease susceptibility including obesity, diabetes, cardiovascular and reproductive diseases, all with their own substantial societal costs [52,64–66]. DDP refers to the shallow invasion of the placental bed into the maternal decidua and myometrium including incomplete remodeling of the uterine spiral arteries [62,67]. The latter is a vital event during which under normal conditions the endothelial lining of the spiral artery walls are remodeled to accommodate the inundation of maternal blood flow starting in the second trimester [68]. Spiral arteries that fail to undergo this vascular remodeling are not only narrower in diameter, but also remain excessively responsive to vasoconstrictive compounds such as stress hormones (see endnote 2). The etiological trigger(s) leading to DDP are thought to involve either early placental oxidative stress which triggers an inflammatory response, or vise-versa, an atypical inflammatory maternal immune response to the fetal-placental unit leading to placental oxidative stress and further inflammation [69,70]. The difference between a normal and an affected pregnancy is a matter of degrees on a continuum with individual

biological and behavioural variability nested within the social and physical environment [12,24–26,68,69,71–73].

2.2 The Physical Environment: Particulate Air Pollution

Air pollution is a general term used to describe the presence of agents (particulates, biologicals, chemicals) in outdoor or indoor air that negatively impact human health. Several common air pollutants have been associated with APOs, including carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone, particulate matter (PM) and polycyclic aromatic hydrocarbons (PAHs) [1]; however, attention has focused on the latter two compounds showing strong molecular evidence of cytotoxicity, mutagenicity, DNA damage, oxidative stress and inflammation [55,74–79]. While the observed risks of APOs in relation to air pollution tend to be modest, the population attributable risk can be quite large due to the pervasiveness of exposure to the general population [9]. Significant risks have been observed even in settings with relatively low ambient air pollution exposure [80,81]. Therefore, a small increase in risk can have a large public health impact. PTB and FGR are major risk factors of perinatal mortality and serious infant morbidities contributing to increased health care and societal costs [82–87].

Particulate matter (PM) is a complex mixture of varying chemical and physical properties. It is defined according to particle size into the inhalable coarse fraction (PM_{10}, 2.5-10μm), the fine respirable fraction ($PM_{2.5}$, ≤ 2.5μm) and the ultrafine fraction (UFP, ≤ 0.1μm). Their ubiquity and recognized human health risks have deemed them as toxic [88,89]. Characterizing PM by particle size is important for several reasons. First, particle size dictates the location of deposition in the respiratory system [88,90]. Second, particle size can give some indication of its general source and behaviour. For example, PM_{10} is mainly derived from mechanical processes such as windblown soil, pollen, minerals and dust from roads, farms and industrial operations. PM_{10} tends to gravitationally settles in a matter of hours to days. Conversely, $PM_{2.5}$ is a primary by-product of combustion and atmospheric reactions with precursor gases such as SO_2, nitrogen oxides, ammonia and volatile organic compounds (VOCs). $PM_{2.5}$ can remain suspended in air for days to weeks, and are consequently more prone to long-range transport. Precipitation accounts for 80-90% of $PM_{2.5}$ removal from the atmosphere [88]. Third, the chemical composition is markedly different between PM_{10} and $PM_{2.5}$ mixtures. Derived mainly from the Earth's crust, PM_{10} typically contains oxides of iron, calcium, silicon, and aluminum; whereas $PM_{2.5}$ mixtures derived from anthropogenic combustion sources are mainly composed of

sulphates, nitrates, ammonium, trace metals, elemental carbon and organic hydrocarbons (e.g. PAHs) [88]. Chemical differences and relative proportions also differ within the PM_{10} and $PM_{2.5}$ mixtures with regional (urban-to-rural) and inter-urban (urban-to-urban) differences as well as intra-urban spatial variation [88,91–93]. Therefore trimester and demographic differences in residential mobility and intra-urban population differences are important study design issues to consider [94,95]. Finally, PM_{10}, $PM_{2.5}$ and UFPs differ by their toxicological mechanisms, such as their oxidative potential, which may reflect their differences in size, surface area and/or their chemical constituent compositions, although they tend to be correlated [76,92,96,97]. Transition metals such as copper, nickel, lead, chromium, iron, vanadium and cobalt among other metals are variably present in ambient air absorbed to $PM_{2.5}$ [92,93]. Their direct oxidative action or redox potential to create reactive oxidative species (ROS) is one possible mechanism as to how PM induces oxidative DNA and protein damage [78,97].

There is accumulating evidence that suggests UFPs may be the fraction of PM responsible for many of the adverse health effects reported in air pollution studies [78,79,97,98]. UFPs are a small proportion by mass but make up a large proportion in particle number and have gone either unmeasured or misclassified as $PM_{2.5}$ [88,98]. Their small size facilitates better tissue penetration deep into lung alveoli and into epithelial cells restricting their clearance via macrophage phagocytosis [98]. Animal studies have shown that UFPs can translocate across the lung epithelium into blood circulation and accumulate in other organs, including the liver, spleen, kidneys, heart, brain and reproductive organs [98]. The high surface area of UFPs favours the absorption of PAHs and possibly transition metals which has shown to localize in the mitochondria inducing major structural damage. This could be a possible explanation to UFP's exhibited higher oxidative potential compared to larger PM fractions of the same material [79]. Recent attention has been given to pro-inflammatory and endocrine-disrupting properties of diesel emissions, a major source of UFPs in ambient air [31,99–101].

Polycyclic aromatic hydrocarbons (PAHs) are organic substances that constitute a class of over 100 individual chemical compounds made up of carbon and hydrogen atoms formed into rings [102]. While toxicological data exist for individual PAHs (benzo[a]pyrene being the most commonly used PAH indicator), they almost always occur as complex mixtures (e.g. soot, tobacco smoke, creosote, diesel exhaust) [103]. Thus it is difficult, and arguably futile, to assess the toxicity of individual PAH components only to be compounded

by the likelihood of interactions [75,104,105]. Combustion of organic matter and fossil fuels are the main source of atmospheric PAHs with their distribution and magnitude concentrated along transportation corridors (road and rail) and land-use areas with heavy industrial activities. However, main stream and environmental tobacco smoke (ETS) remain a leading source of PAH exposure [106]. PAHs are generally non-volatile (i.e. stable) and have low water solubility. As a consequence, PAHs often bind to $PM_{2.5}$ and UFP in the atmosphere. Residency times in the atmosphere depend on weather conditions, PAH molecular weight and the emission source (e.g. stack vs. tailpipe) with atmospheric deposition as the main source of PAHs to soil, vegetation and surface water. Once in aquatic systems, PAHs are often found absorbed to suspended particles or bound to sediments settled on the bottom where they persist or are slowly biodegraded by microorganisms. While PAHs can bioaccumulate in some aquatic and terrestrial organisms, they tend to not biomagnify in food systems due to their metabolism in higher order species [102,106]. However, it is the inefficient clearance and action of the highly reactive PAH metabolites that are suspected to cause cytotoxicity, mutagenicity, DNA damage, oxidative stress and tumourgenesis [75,106].

Much of the work elucidating the mechanisms in which PM and PAHs elicit adverse cellular effects have been conducted using cardiovascular disease (CVD) and lung cancer as models [76–78,97,107–109]. Although seemingly different diseases from APOs, there are several similarities between them. First, both APOs and CVD related outcomes are associated with PM exposure levels which vary by SES [40,110,111], but are also associated with other socially patterned risk factors such as smoking, poor or inadequate diet, psychosocial stress, obesity and diabetes [12,112–114]. CVD and APOs also share many other risk factors such as the presence of systemic inflammation and pre-existing hypertension. Interestingly, PIH/PE is a risk factor for maternal CVD later in life and also in the offspring if affected by IUGR [115–117]. CVD and disorders of DDP have similarly affected cellular tissues in their respective target systems (i.e. endothelial cells of the cardiovascular system and in the highly vascularised placenta) which are particularly susceptible to oxidative and inflammatory injury [97,118]. High plasma homocysteine concentrations are positively associated with vasculopathy and infarction in the placental-uterine and coronary systems increasing the risk of spontaneous PTB and CVD events respectively [119,120]. Fittingly, high density lipoprotein cholesterol may be protective against spontaneous PTB and CVD events [120,121]. Finally, PM and PAH-induced

mutagenicity, cytotoxicity, DNA damage and oxidative stress linked to lung cancer have also been observed in the fetal-placental unit [122,123], and exposure early in pregnancy may contribute to the risk of congenital anomalies and early (sub-clinical) pregnancy loss [124–127].

2.3 The Social Environment: Socio-economic Status, Diet, Smoking & Allostatic Load

The social environment plays a significant role in maternal and perinatal health with indicators of low socio-economic status (SES) consistently among the strongest predictors of adverse pregnancy outcomes [10–12]. The causal pathways in which SES contributes to APOs and ill health in general can be conceptualized in terms of 'downstream' or mediating exposures, stresses and behaviours acting on the individual through 'upstream' society-level determinants such as poverty, poor education, income inequality and social discrimination/marginalization over the lifespan [12]. Indicators of low SES associated with PTB and FGR include maternal anthropometry (pre-pregnancy BMI, height, gestational weight gain), nutrition and micronutrient status, cigarette use, genital tract infections and inflammation, cocaine and other drug use, physically demanding work, quantity and quality of prenatal care, and psychosocial factors including anxiety, depression and stress (e.g. lack of social, familial, and marital support, poverty or financial hardship, physical/verbal abuse, neighbourhood crime) [12,24,26,54]. For the purpose of this review, the focus here will be on three that engage with the oxidative stress and inflammation pathways to potentially interact with exposure to particulate air pollution. They include: 1) a diet-micronutrient pathway [55,128–131], 2) cigarette smoke exposure [35,132–135], and 3) allostatic activation of the HPA-axis and corresponding glucocorticoid production [47,72,136–138].

Nutrition and diet can influence perinatal health in opposing directions. Poor/under-nutrition such as high fat/calorie dense food and low micronutrient intake is more prevalent among women from low SES backgrounds which may partly explain higher rates of some APOs [12,139–142]. Conversely, adequate diet and micronutrient status provides resilience against oxidative stress and inflammation caused by various exposures including air pollution, allostatic stress, infection or smoking [55,118,128,129,131,143]. Maternal exposure to mainstream or environmental cigarette smoke during pregnancy is associated with numerous APOs including congenital anomalies [127,144–146]. Their exposure prevalence is associated with indicators of low SES as well as other socially-patterned risk factors [147–149], and remains one of the most modifiable risk factors with potential for beneficial intervention. Other risk factors associated with low SES such as obesity,

(gestational) diabetes and hypertension [13,113,150] also engage the oxidative stress and inflammatory pathways and could therefore also potentially interact with PM exposure to increase susceptibility to adverse effects as evidenced in studies of cardiovascular health [114,151,152]. Recent studies have observed increased risks of preeclampsia and gestational diabetes associated with measures of air pollution [153–156] with one study showing positive effect modification by pre-existing and gestational diabetes [154]. Evidence shows that chronic life stressors associated with low SES at multiple levels of organization (individual, household, community) result in a cumulative biological toll on the body affecting multiple systems and increasing susceptibility to numerous ailments [21,157–160] including APOs [15,26,161,162].

The concept of allostasis and allostatic load/overload has been proposed to describe the individual stress response to an event as a necessary and adaptive process thereby removing the implicit negative connotation attached to the term 'stress' [163]. Stress can be positive or tolerable when it improves function and performance and may have long-term adaptive benefits. However, this may depend on available coping resources such as one's psychological resistance, resilience and ability to recover. Negative or toxic stress occurs when real or perceived environmental/social demands, or the anticipation of such, become too extreme or unpredictable thereby exceeding one's (perceived) ability to cope (e.g. no sense of control, adverse childhood experiences and other forms of trauma) [164,165]. Therefore, allostasis is the multisystem biological response that promotes adaptation using system mediators such as cortisol, (nor)epinephrine, vasopressin, renin, and glucagon [165,166]. Whereas allostatic load and overload is the cumulative toll (wear and tear) on biological systems after prolonged or poorly regulated (hyper/hypo activated) allostatic responses. For example, the cardiovascular system is extremely sensitive to stress in terms of increased blood pressure; however, metabolic disorders such as diabetes and obesity as well as immune function impairment are also linked to chronic stress. Furthermore, lifestyle coping mechanisms as a response to chronic stress have the ability to either buffer or exasperate the effect (e.g. exercise, diet, sleep, social interactions or lack thereof) [163]. Therefore in light of the above, it is our belief that the fetal-placental unit is the site where the physical and social environments converge and interact to influence reproductive health which we describe further below.

Figure 1 illustrates the inter-connectedness between particulate air pollution (PM/PAH) and SES on how they may act discretely or in a combined manner to yield APOs.

Using Figure 1 as a guide, the following text will review the two major mechanisms (oxidative stress and inflammation) through which the physical and social environments are believed to negatively affect the fetal-placental unit and how they may combine/interact to lead to the multi factorial nature of APOs.

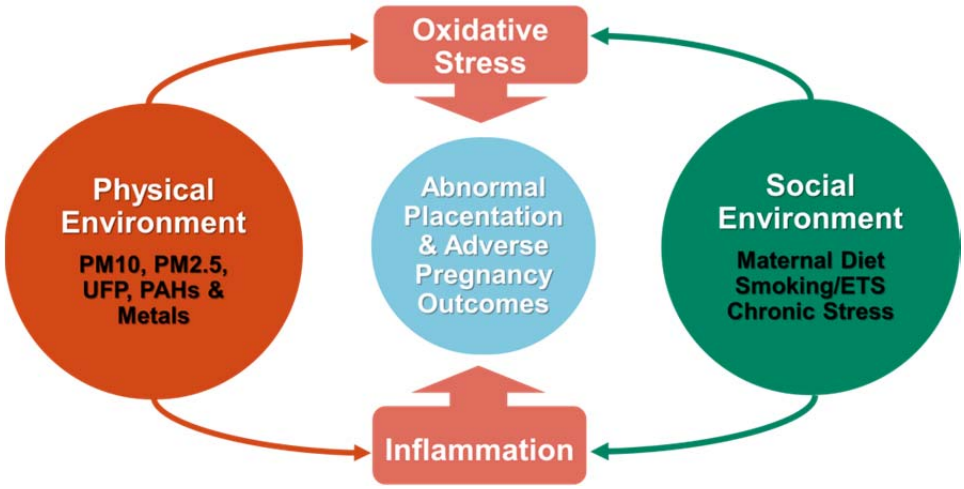

Figure 1: A conceptual framework of the shared mechanisms of socio-economic determinants and particulate air pollution exposure contributing to adverse pregnancy outcomes

The physical environment (orange) consisting of particulate air pollution and the social environment (green) consisting of community and individual-level social factors/stressors converge to affect the fetal-placental environment (blue) via oxidative stress and inflammatory mechanisms potentially leading to adverse pregnancy outcomes.

3.0 Biological Mechanisms Leading to Adverse Pregnancy Outcomes

3.1 Oxidative Stress

Aptly known as "The Oxygen Paradox", oxygen is both essential and toxic to the multicellular aerobic organisms whose very evolution was dependent on leveraging this anaerobic waste by-product into a higher energy producing advantage [167]. Observed in all mammals, a steep oxygen tension gradient from 20% in our atmosphere to 3-4% oxygen concentration in most internal tissues is the primary defense against oxidative damage. Secondary and tertiary layers of protection include antioxidant defenses as well as damage removal, repair and apoptotic response systems [168,169]. These genetically adaptive responses are upregulated in the presence of reactive oxygen species (ROS) generated as natural by-products of cellular aerobic metabolism and exposure to various toxins. Oxidative stress occurs when there is an imbalance between pro- and antioxidant capacity.

For example, superoxide is the most common intracellular ROS in mammals. It is produced by the mitochondria as a metabolic by-product but also from the metabolism of

various growth factors, drugs and toxins by oxidizing enzymes such as NADPH-oxidase and cytochrome P450 (CYP450). Superoxide is reduced by superoxide dismutase (SOD) into hydrogen peroxide (H_2O_2) which is then further reduced into water by glutathione peroxidase (GPx) and catalase. Under normal physiological conditions H_2O_2 acts as intracellular secondary messengers; however, it's accumulation along with superoxide can react with free iron ions or nitric oxide to form highly toxic hydroxyl ($OH\cdot$) or peroxynitrite ($ONOO^-$) ions respectively [70,168]. Free iron is a common metal found absorbed to PM, and the antioxidant heme oxygenase-1 (HO-1) facilitates its conjugation and removal through the increased availability of ferritin thereby preventing the formation of reactive hydroxyl molecules [92,170–172]. Deficiencies in HO-1 have been associated with several APOs such as recurrent miscarriage, FGR and preeclampsia [171,172].

Common antioxidants include enzymatic (e.g. SOD, GPx, catalase, HO-1) and non-enzymatic compounds (e.g. vitamin C and E, glutathione, β-carotene, ubiquinone) [118]. Genetic polymorphisms and/or micronutrient deficiencies in antioxidant enzymes precursors can impair antioxidant capacity, while chronic exposure to toxicants, psychosocial stress, bacteria, viruses and other inducers of inflammation can foster pro-oxidant burden [70,77,118,172]. Oxidative stress is unavoidable; however, under optimal conditions the presence of ROS leads to homeostatic adaptation and are safely removed. Failure to effectively manage oxidative stress can result in altered cellular function as excess ROS degrade lipids, proteins and DNA potentially initiating pathological processes. Refer to [168] for an extensive review on the role of cellular ROS in pregnancy outcomes.

3.2 Inflammation and Immunologic Alterations

It is well recognized that the maternal immune system plays a central role throughout the entire pregnancy, from pre-implantation to parturition, and is influenced by the inflammatory response of the mother to her environment as well as to her partner (see endnote 3). Alternative to previously hypothesized [173], the maternal immune system is not passive or suppressed during implantation and development of the semi-allogeneic placenta and fetus. Rather, it exerts executive influence on the establishment and progression of the pregnancy as an immune-mediated quality control mechanism to maximize maternal and offspring health [44,173]. This is achieved by favouring pro- or anti-inflammatory environments at different times during pregnancy for different purposes. For instance, implantation, initial placentation and parturition are characterized by a pro-inflammatory environment whereas an anti-inflammatory state prevails for most of mid-

gestation [174]. The favoured localized immunological response however is highly modified by the infectious, inflammatory, stress, nutritional and metabolic status of the individual and thus can be influenced by environmental agents such as PM [175–177] and/or available coping, social and nutritional resources [44,128,164,178]. Therefore, inflammation is believed to be one pathway involved in both PM and SES-mediated APOs.

Chronic and acute inflammation is a complex response process mediated by a real or perceived attack from foreign substances. The innate immune response is the rapid automatic response to externally originating (exogenous) substances such as pathogens, but also from internal (endogenous) danger signals including products of trauma, ischemia, necrosis or oxidative stress [179]. The response includes the release of pro-inflammatory signaling cytokine proteins such as interleukins IL-1β, IL-6 and tumour necrosis factor (TNF-α) which serve to recruit neutrophils to affected tissues. However, the recruited neutrophils release ROS and hydrolytic pro-inflammatory enzymes (inducible nitric oxide synthase (iNOS), cyclooxygenase (COX-2) and prostaglandins ($PG\text{-}E_2$)) which disturb normal cells in addition to affected tissues which in turn leads to increased ROS and oxidative stress [180,181]. The placenta is a multi-functional organ and its role at the maternal-fetal interface as the main producer of endocrine steroid and protein hormones as well as the immunologic barrier between mother and fetus positively interact for the success of the pregnancy [44,173]. This is achieved through a non-linear series of positive and negative feedback pathways with the stimulation or suppression of molecules with pro- and anti-immunosuppressant properties (interleukins, galectins, placental growth factor, and human chorionic gonadotropin (hCG)) [182–184]. The production of these cytokines, chemokines and other immune-regulatory agents mediate the coordination, migration and function of several maternal immune cells (e.g. uterine natural killer cells (uNK)) that participate in early pregnancy events such as endometrial receptivity of embryo implantation, tissue remodeling, immune tolerance and vascular adaptation to invading placental trophoblast cells [44,182–184]. Interference or aberrant production/secretion of these substances by various stressors including infection, toxins and those acting through the HPA-axis may result in the impaired maternal immune response leading to the hallmark DDP syndrome complications described above (early pregnancy loss, PIH/PE, PROM, FGR, premature labour, Figure 2) [44,61,69,134,175,185–187].

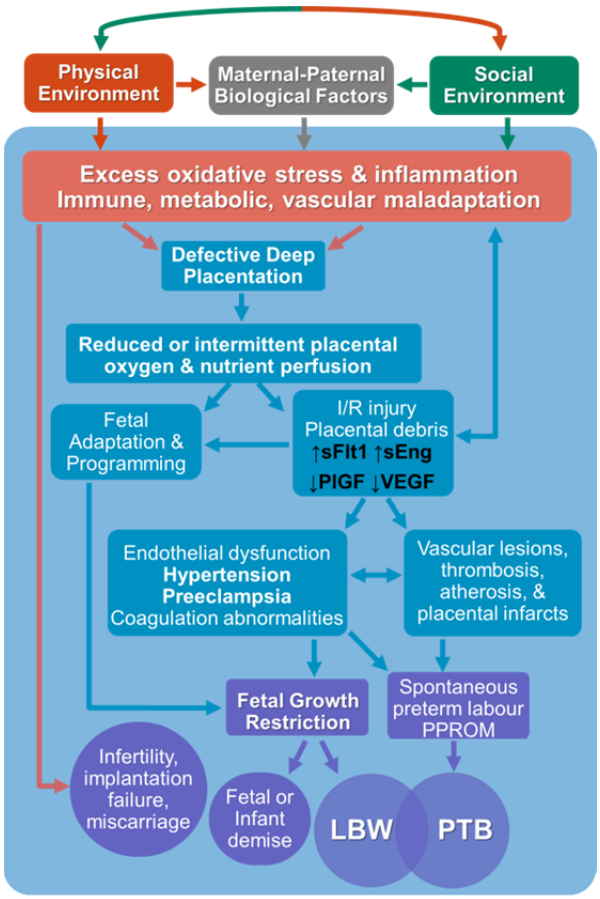

Figure 2: Proposed pathways contributing to adverse pregnancy outcomes
The co-presence of maternal and paternal biological factors can result in protection or increased susceptibility to the interaction with the physical and social environments. Cumulative negative exposures early in pregnancy resulting in excess oxidative stress and inflammation may cause a cascade of events leading to defective deep placentation. Depending on the degree of severity, the reduced transplacental perfusion can result in various pathologies associated with a range of obstetric complications and outcomes [60,61,69,70].

3.3. Mechanisms of Oxidative Stress and Inflammation Involved in Adverse Perinatal Outcomes

3.3.1 Impaired fertility and (recurrent) miscarriage

Due to immortal time bias, miscarriage is not easily measured in population or cohort studies without careful design methodologies [188,189]; however, associations between infertility and air pollution have been made [190,191]. Oxidative stress has shown to have a direct effect on fertility and embryo development. For example, obese mice showed increased ROS synthesis and oxidation in oocytes with a reduced ability of zygotes to develop to the blastocyst stage providing evidence that impaired cellular antioxidant capacity can limit successful ovulation and fertilization [118]. Dividing mitotic cells are particularly sensitive to oxidative damage and are shown to enter a transient growth-arrested state as a protective mechanism until the stress has passed. Thus, severe or chronic oxidative stress may hamper cell division or cause cellular necrosis reducing or terminating embryo viability [72,169]. Alternatively, an exaggerated inflammatory state via a viral, toxic and/or allostatic load could lead to maternal immune maladaptation to

conception leading to restricted trophoblast stem cell accumulation in the early peri-implantation embryo responsible for the production of hormones that enables successful implantation (Figure 2) [44,72].

Oxidative stress is implicated in first trimester miscarriage from premature placental perfusion of maternal oxygenated blood and accompanying ROS into the early embryonic environment [192]. Early embryo development occurs in a low oxygen state, and it is not until the tenth to twelfth week of gestation that maternal blood begins to gradually infiltrate the intervillious space of the yet fully developed placenta. The limited oxygen environment is thought to act as a protective mechanism against the deleterious and teratogenic effects of ROS on early stem cells at a time of extensive cell division [64,138]. This early hypoxic environment also plays a vital physiological role in placental cell type differentiation switching from proliferative villous cytotrophoblasts into invasive extravillious trophoblast (EVT) important in spiral artery remodeling [193]. At the end of the first trimester, oxygen tension rises sharply which coincides with the infusion of oxygenated maternal blood into the placenta and triggers an apoptotic cascade that serves to establish the definitive discoid placenta. However, in 70% of early miscarriage cases EVT invasion is insufficient allowing for the premature onset of maternal intraplacental circulation and its consequential burst of ROS on the conceptus [70,192]. Severe cases may result in pregnancy failure while more modest cases may initiate fetal-maternal adaption to impaired spiral artery remodeling leading to the pathology for further complications later in pregnancy such as PIH/PE (Figure 2) [69,70,193].

3.3.2 Pregnancy induced hypertension, preeclampsia, and prelabour rupture of membranes

While oxidative stress and inflammation are conditions of normal pregnancy, they are consistently elevated in cases of PIH/PE and both are central in its pathology. PIH/PE stems from a defect in early trophoblast invasion insufficient to fully convert the spiral arteries into low-resistance channels [68,194]. The retention of smooth muscle cells remains active to circulating vasoconstricting agents such as stress hormones (e.g. glucocorticoids) and other stimulants. The diminished, but more importantly, the intermittent perfusion of maternal blood into the intravillious space produces transient hypoxia resulting in a chronic ischaemia-reperfusion (I/R) type injury. This further provokes ROS synthesis and excess shedding of placental microvesicles which have pro-inflammatory, anti-angiogenic and procoagulant activity initiating endothelial dysfunction [68–70]. Elevated circulating levels of placental debris and ROS biomarkers in the placental tissues of preeclamptic women are

well documented [68,179,194]. Similarly, PROM can be considered part of the DDP syndrome but may represent a phenotype resulting from a less severe DDP pathophysiology compared to preeclampsia [61,62]. Excess oxidative stress arising from multiple causes (infection, inflammation, smoking, cocaine use) have been implicated in PROM in addition to its role in DDP [70]. Both PIH/PE and PROM are leading causes of preterm birth while PIH/PE is a major risk factor for FGR (Figure 2) [69]. Deficiencies in HO-1 have been associated with various APOs such as recurrent miscarriage, FGR and preeclampsia as well as morphological changes in the placenta and elevations in maternal blood pressure. The bioactive metabolites of HO-1, CO and bilirubin, may protect against preeclampsia through their vasodilatory properties and the suppression of the anti-angiogenic factor sFlt respectively [171,172].

3.3.3 Fetal growth restriction

FGR has many causes, however often arises from placental insufficiency due to compromised supply of oxygen and nutrients to the fetus which may have both short and long-term health consequences on the offspring [51,82,195]. FGR is strongly associated with early onset or more severe cases of preeclampsia, and there is a clear etiological link between IUGR and DDP as it involves abnormal placentation and reduced uteroplacental blood flow (Figure 2) [62,70]. Alternatively, perturbed calcium homeostasis can induce chronic low-level stress within the endoplasmic reticulum leading to suppressed protein synthesis and a reduced growth trajectory of the placenta [70]. Cadmium, an environmental toxin and highly present in cigarette smoke, is a major antagonist of cellular calcium activities (transport, uptake, binding), as well as the transfer of other nutrients and zinc homeostasis within the placenta [134,185,196]. Furthermore, cadmium is a known endocrine disruptor shown to impair hormone synthesis in the placenta including progesterone and leptin [49,175,186]. Both smoking and air pollution exposure were associated with lower birth weights along with low blood progesterone levels and high placental cadmium concentrations compared to a non-exposed control group [135].

3.3.4 Spontaneous preterm labour and birth

Inflammation is proposed as one potential mechanism leading to spontaneous preterm labour, both with intact membranes or PROM. The classification of patients who deliver preterm can be categorized into two non-mutually exclusive clusters; those who present with inflammatory lesions (e.g. acute chorioamnionitis and funisitis) and those with

vascular lesions who tend to have longer gestational periods [61]. The consequence of uteroplacental ischemia as a result of such lesions will depend on the severity, the timing and duration of the insult. While a complete blockage of uterine arteries will lead to fetal death, less severe ischemia will result in different clinical phenotypes as a result of adaptive mechanisms for fetal survival. This may include fetal growth restriction if chronic underperfusion of oxygen and nutrients persists, the onset of maternal hypertension to sustain or increase uterine blood flow, and/or the initiation of preterm labour as a maternal/fetal adaptation to continued growth restriction *in utero* (Figure 2) [61,197]. Cardiovascular lesions indicating thrombosis and atherosis are shown to be indirectly caused by exposure to $PM_{2.5}$ and UFPs via inflammatory and /or oxidative injury [97].

4.0 The Physical and Social Environment and their Relation to Adverse Perinatal Outcomes

4.1. PM-induced oxidative stress and inflammatory mechanisms

Exposure to $PM_{2.5}$ and its constituents, including PAHs and metals, induce oxidative stress and inflammation in many biological systems through various means (Figure 3) [48,77–79,97,176,177,198]. One method is the direct generation of ROS from free radicals and oxidants on particle surfaces including soluble transition metals such as iron, copper, chromium and vanadium. As mentioned above, free iron can react with available superoxide or hydrogen peroxide to form highly reactive hydroxyl radicals [70,77]. PAHs and other organic molecules absorbed to $PM_{2.5}$ and UFPs may account for a large proportion of their oxidative potential due to their ability to enter the cell and disrupt the mitochondria [79]. Altered function of mitochondria may produce excess quantities of NADPH-oxidase which in turn generates large amounts of cellular superoxide, a process already in overdrive throughout pregnancy but particularly in the first trimester [70,77]. Interpolated ambient PM_{10} exposure was shown to be negatively associated with the number of placental mitochondrial DNA, a molecular marker of mitochondrial disruption and inflammation. This association was reversed with increasing distance from major roads, a proxy for traffic-related air pollution [48].

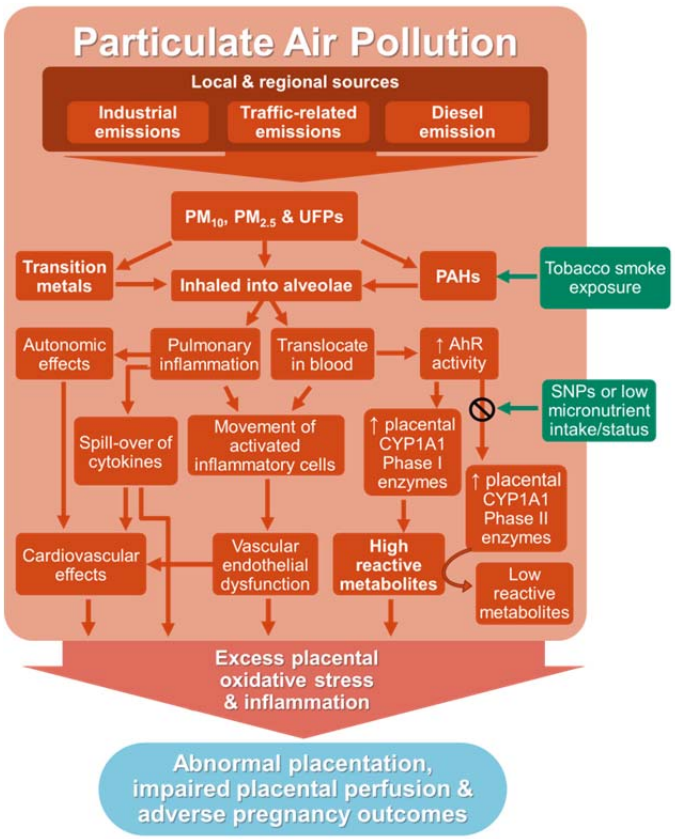

Figure 3: Proposed pathways of particulate air pollution contributing to oxidative stress and inflammation leading to adverse pregnancy outcomes
Exposure to PM and its associated constituents of transition metals, PAHs and other organic molecules affect the cardiovascular and metabolic systems which are highly active throughout pregnancy. For example, detoxification of PAHs and other organic toxins activate AhR signalling resulting in additional oxidative stress if antioxidant defenses are limited or impaired [55,79,98,108,109,199].

Alternatively, PM/PAH mediated oxidative stress can be induced by the activation of the inflammation system. Immunotoxic compounds can promote the release of pro-inflammatory cytokines, TNF-α and COX-2, which in turn act in a positive feedback loop to generate more ROS and oxidative stress [77]. For example, modelled PM_{10} and $PM_{2.5}$ exposure has been positively associated with elevated C-reactive protein (CRP) levels, a biomarker of systemic inflammation, in both maternal first trimester blood and fetal cord blood in a dose-dependent manner [176,200]. CRP is produced in the liver and part of the acute-phase response released during inflammatory reactions from cytokines produced in the lungs. Raised CRP is a risk factor for cardiovascular disease as a marker of unstable atheromatous plagues leading to thrombosis and ischemic events [97]. Exposure to diesel exhaust in healthy human volunteers produced defined health effects in addition to pulmonary inflammation, including systemic inflammation, pro-thrombotic changes and other cardiovascular effects consequent of pro-inflammatory events [99,201]. This hyper pro-inflammatory state, along with oxidative stress, is hypothesized to contribute to several APOs [69,70,174,181,202].

Indirectly, the cellular detoxification of PAHs can induce oxidative stress and cytotoxicity by forming potent ROS metabolite by-products. Specifically, PAHs and other organic xenobiotics (notably PCBs and dioxins) are detoxified by the cytochrome P-450 (CYP) superfamily of Phase I and Phase II metabolizing enzymes. The expression of these enzymes are highly modulated by genetic polymorphisms, steroid/sex hormones such as glucocorticoids, insulin, estrogens and progesterone, and micronutrient/dietary deficiencies [74,75,128,203,204]. Furthermore, hypoxia, infection and inflammation are shown, in general, to down-regulate CYP enzymes which may affect the clearance and bioavailability of growth factors, hormones, drugs and toxins [203,205]. CYP has numerous isoforms which are expressed in many tissues especially the liver. CYP1A1 is the only isoform also significantly expressed in the placenta throughout pregnancy responsible for metabolizing steroid/sex hormones, growth factors and fatty acids in addition to toxins [75]. These exogenous and endogenous substances act as ligands to activate the aryl hydrocarbon receptor (AhR), a transcription factor that mediates the biotransformation of such ligands (PAHs, estradiol, etc.) into more polar and bioavailable metabolites by up-regulating CYP enzymes (see endnote 4). However, certain metabolites of PAHs (e.g. o-quinones, arene oxide and diol epoxide) bind to DNA, RNA and protein macromolecules to form toxic adducts that disrupt DNA replication and are considered mutagenic [72,75]. Such DNA adducts have been found in newborn cord-blood positively correlated with maternal exposure to PAHs [50]. PAHs have also shown to significantly decrease the accumulation of trophoblast stem cells in the early placenta thereby limiting their differentiation into other cell types vital for hormone synthesis and ongoing placental development, a process that could contribute to DDP [72]. Direct prenatal exposure to airborne PAHs has been associated with FGR with an increased exposure-related risk in the first trimester [206,207]. Secondary (Phase II) metabolizing enzymes are required to further detoxify reactive PAH-metabolites, to which their inefficient clearance results in prolonged exposure leading to sustained cytotoxicity and mutagenicity. Phase II enzymes include glutathione s-transferases (GSTs), UDP-glucuronosyltransferases (UGTs), NAD(P)H-dependent quinone oxydoreductase-1 (NQO1), aldehyde dehydrogenase-3 (ALDH3) [75,205].

4.2 Maternal Diet and Micronutrient Intake

Adequate diet and micronutrient status provides resilience against oxidative stress and inflammation caused by various exposures including air pollution, allostatic stress, infection or smoking (Figure 4) [55,118,128,129,131,143]. Many micronutrients such as

essential trace metals are vital co-factors in several antioxidant enzyme systems. For example, copper and zinc are necessary in the production of SOD. Similarly, selenium and its incorporation into the amino acid selenocysteine is required for the functionality of all selenoenzymes, including GPx and GST. Thus, selenium is essential in several aspects of human health, particularly conditions involving oxidative stress and inflammation such as CVD, immune function, cancer and reproduction, but also thyroid regulation and brain diseases [208,209].

ROS may have direct effects on oocyte quality and appears to be modulated by dietary antioxidant supplements [118]. Women who are obese tend to have higher rates of infertility that correlate with increased levels of oxidative stress biomarkers in their blood as excess glucose availability leads to higher mitochondrial ROS synthesis [70,118]. Selenium deficiency and corresponding reduced GPx activity has been documented in cases of recurrent miscarriage and spontaneous abortions [210–212], and has also been associated with preeclampsia and preterm birth [213,214]. However, given the supposed role of oxidative stress in preeclampsia, treatment with certain antioxidants (notably vitamin C and E) has not produced reliable preventative results in experimental trials [69]. One hypothesis is that inappropriate antioxidant regiment and/or administration too late in gestation are responsible and new therapeutic candidates include melatonin and selenium [118]. Interestingly, national programs in Finland and New Zealand fortifying food with selenium has been associated with significant reduction in the rate of preeclampsia [215].

Oxidative stress negatively affects the placental transport of amino acids and glucose [45]. Furthermore, fatty acids and low density lipid (LDL) cholesterols necessary for the placental synthesis of oestrogens and progesterone are particularly vulnerable to oxidative injury [216]. Regulation of placental nutrient transport is controlled by several different mechanism, including imprinted genes, placental signaling pathways, various cytokines and hormones such as insulin, leptin, glucocorticoids and oestrogens (for review see [45]). The major placental transfer mechanisms include: simple diffusion of lipophilic substances (e.g. oxygen, CO_2, fatty acids, steroids, fat soluble vitamins, anesthetic gases), restricted diffusion of hydrophilic substances, facilitated diffusion via a membrane bound carrier (e.g. glucose and other carbohydrates), and active transport which requires energy (e.g. amino acids, iron, calcium, and other divalent cations) [45,217]. Placental physiology, including spiral artery remodeling and placental villous surface area are major determinants dictating

placental transport capacity, and the degree of placental developmental disruption correlates with the severity of obstetrical complications associated with DDP [51,62].

Nutrition and diet can influence perinatal health in opposing directions (i.e. it can be an antagonist or agonist). Poor/under-nutrition such as high fat/calorie dense food and low micronutrient intake is more prevalent among women from low SES backgrounds which may partly explain higher rates of some APOs [12,139–142]. On the other hand, good nutrition and supplemental vitamin intake is capable of reducing the toxicity of everyday environmental stressors as well as preventing certain APOs and congenital anomalies as shown with the successful reduction of neural tube defects with folic acid [128,143,218]. Nutritional and/or genetically-induced deficiencies in folate and vitamins B_6 and B_{12} can disrupt the homocysteine-to-methionine pathway resulting in hyperhomocyteinemia (HHC), a known risk factor of cardiovascular morbidities (thrombosis, lesions and infarcts) and markers of oxidative stress [54,119,219,220]. HHC may similarly affect the highly vascularized placenta, and has been associated with decidual vasculopathy and preterm birth [54,120]. Omega-3 fatty acids abundant from eating salmon was shown to improve markers of oxidative stress [221], which may impart neurodevelopmental resilience against stressors [222,223]. Dietary phytophenols from fruits, vegetables, herbs and spices have shown to have antioxidant and anti-inflammatory properties capable of reducing infection-induced inflammatory and contractile pathways in human gestational tissues [129]. Significant differences in pregnancy outcomes between Dominicans and African Americans both exposed to similar levels of PAHs in New York city neighbourhoods were thought to be due to healthful dietary/cultural practices in the Dominican immigrant population [206].

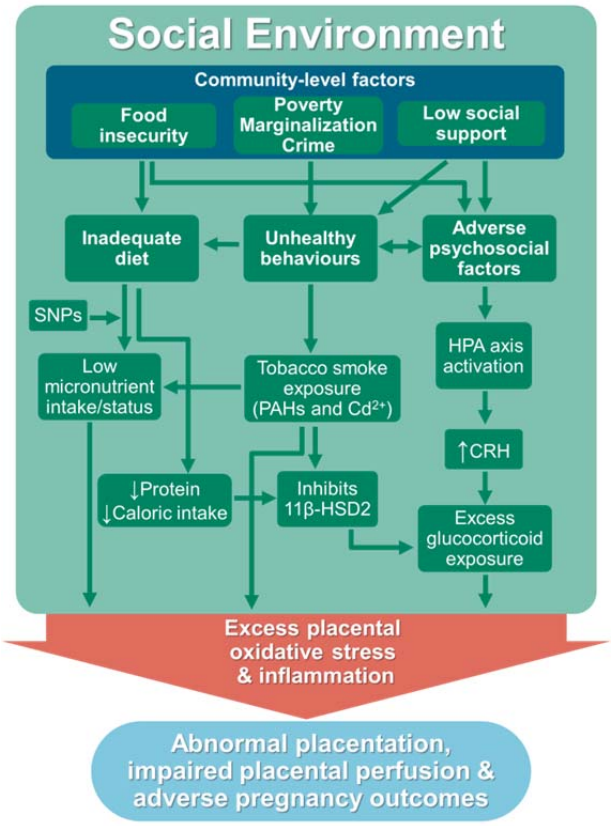

Figure 4: Proposed pathways of how the social environment interacts to produce excess systemic and placental oxidative stress and inflammation leading to adverse pregnancy outcomes
The pregnant woman is nested within and influenced by neighbourhood/community-level factors which can exasperate or buffer the individual-level biological and behavioural factors [24,26,54,128,224,225].

4.3 Maternal Smoking and Environmental Tobacco Smoke (ETS) Exposure

Maternal smoking during pregnancy and exposure to ETS remain to be two modifiable risk factors with the greatest potential for beneficial interventions (Figure 4). Their association with numerous APOs including congenital anomalies is well documented [127,144–146], as have their associated prevalence with indicators of low SES and other socially-patterned risk factors [147–149]. The mechanisms involved leading to APOs have been well reviewed [132,134]; however, it's notable that the two main toxins present in tobacco smoke are also constituents of PM (PAHs more so than cadmium). Cadmium (Cd) exposure readily interferes with the active transport of essential minerals to the fetus, particularly zinc and calcium [46,135,196,226–228]. Cadmium and lead (Pb) exposure has also been shown to reduce glycogen concentrations thereby potentially limiting available glucose to the fetus [229]. Cadmium has shown to disrupt placental leptin synthesis, a hormone with several vital functions including placental angiogenesis, immunomodulation, amino acid and fatty acid transport as well as fetal pancreatic development important in the regulation of insulin-like growth factors and fetal body fat accumulation [49,51]. Finally, synergistic effects in the generation of oxidative hydroxyl radicals have been observed between tobacco smoke and both ambient $PM_{2.5}$ and diesel exhaust particles specifically

[35]. Interestingly, the counterintuitive association between smoking and lower risk of preeclampsia was recently shown to vary according to the timing and intensity of smoking [230]. It's possible that the increased exposure to carbon monoxide (CO) from smoking in late gestation acts as a vasodilator at the same time inhibits the release of sFlt-1, a hallmark anti-angiogenic factor implicated in the endothelial dysfunction of preeclampsia [115,230].

4.4 Allostatic Stress and Glucocorticoid Exposure

Reviewed elsewhere [163], the brain is the primary target and mediating organ through which SES-related stress pathways are translated to other body systems via the hypothalamic-pituitary-adrenal (HPA) axis. The HPA-axis is actively involved in several biological systems, including the cardiovascular, metabolic, immunological and endocrinal effects in both the mother and fetus to promote allostatic adaptation [165,231]. Here, the neuroendocrine hormones of the HPA axis, corticotrophin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids (GC) respectively, coordinate the biological response via feedback loops. The human placenta is also capable of releasing CRH and other neuropeptides which interact with the HPA axis to regulate the maternal stress response as well as other normal pregnancy functions [47]. Proper levels of *in-utero* glucocorticoids are essential for successful embryo implantation, fetal organ maturation and the initiation of labour with glucocorticoid levels gradually increasing over the course of gestation. Normally, levels of maternal cortisol rise sharply in the third trimester causing the release of placental CRH in a positive adrenal-placental feedback loop. Placental CRH stimulates fetal cortisol secretion which in turn suppresses placental progesterone and activates the release of prostaglandins and oxytocin to promote uterine contractions [47,232]. However, early and increased levels of fetal glucocorticoids can impair growth and predispose to adult-onset diseases [136,233,234]. The placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) protects the fetus from excess endogenous glucocorticoids by converting active cortisol into inactive cortisone. 11β-HSD2 is hormonally regulated making it susceptible to endocrine disruption from chemical and non-chemical stressors such as maternal anxiety, inflammation, infection, cadmium exposure and low caloric intake [136,138,224,235,236]. Placental hypoxia associated with PIH/PE has been shown to suppress 11β-HSD2 activity which may be an adaptive response to counteract compromised fetal growth by allowing more cortisol to reach the fetus for organ development. Low concentrations/activity of 11β-HSD2 and high levels of cortisol

have been associated with PTB and FGR [136,237,238], two outcomes also associated with maternal psychosocial/mental health [233,234,239].

Factors affecting 11β-HSD2 activity that are associated with low SES include allostatic overload leading to the excess production of glucocorticoids that can overwhelm the fetal protective mechanism (Figure 4) [136,231,240]. Indirectly, allostatic load is capable of disrupting the metabolic system, leading to impaired glucose tolerance, insulin resistance, diabetes and/or obesity, all of which are risk factors for various APOs [138,165,231]. General maternal undernutrition and/or a low dietary protein intake has been shown to impair placental glucose transport and inhibit 11β-HSD2 activity in pregnant rats leading to FGR, indicating a possible mechanism through poor diet [224,241]. Additionally, cadmium has also shown to inhibit 11β-HSD2 activity in both human and rodent placentas [225], and prenatal cadmium exposure has been shown to increase fetal corticosterone concentrations in rats which resulted in reduced birth weights [236]. This suggests a possible mechanism from active or passive tobacco smoke exposure or ambient PM exposure [135,242,243]. Collectively, it's possible for the cumulative exposures of PM, smoking, ETS, poor dietary intake and other SES-related factors to interact through the same 11β-HSD2 mechanism to increase the risk of impaired fetal growth (Figure 4).

5.0 Discussion

The ubiquitous exposure to particulate air pollution and its constituents (e.g. PAHs and metals) is but one class of environmental contaminants that can act through oxidative stress, inflammation and/or endocrine disruption to promote developmental toxicity and adverse perinatal health [177,244,245]. Summarized in Figure 2, a perturbed early *in-utero* environment can lead to defective deep placentation resulting in a cascade of fetal-placental adaptive mechanisms contributing to a range of pregnancy complications and adverse outcomes [60]. Here the underlying biological, social and physical risk factors likely intersect to produce excessive or atypical oxidative stress, inflammatory response and biological antagonism in either initiating defective deep placentation pathology and/or contributing to the severity of its phenotype. Socio-economic disparities are known to confound the environmental exposure effects; however, they may also act as potential effect modifiers given their overlapping etiological mechanisms with $PM_{2.5}$ exposure. While the traditional biomedical paradigm that views populations as a collection of independent individuals has yielded useful information regarding risk factors, elucidating the intersecting pathways involved in APOs will require placing individual biologic and

behavioural determinants within the social and spatial context [22,246]. It is now well recognized that SES operates at multiple levels of organization, and neighbourhood or community-level factors can work to either ameliorate or exacerbate certain risk factors [15,24–26]. The healthy migrant paradox exemplifies these effects in which home country, education and neighbourhood qualities combine to modify the expected perinatal outcomes often observed with low income households [161,247].

The SES risk factors that overlap or interact with the PM-mediated mechanisms include smoking, nutrition, and psychosocial stress acting through the HPA-axis and allostatic load. Given this knowledge, interventions aimed at ameliorating these factors may be the best way to counteract the negative influences of low SES and air pollution exposure on fetal development. Maternal smoking continues to be one of the most modifiable risk factors to lower the risk of APOs [134,147]. Furthermore, maternal smoking also tends to interact negatively with nutrient intake and status [133,248]. Smokers in general have poorer nutritional profiles than non-smokers with both behavioural and biological factors independently accounting for the differences in micronutrients such as folate and essential vitamins and minerals [133,248–250]. While smokers tend to have lower dietary nutrient intakes, they also have an accelerated requirement for micronutrients due to increased inflammatory cell turnover caused by the oxidative stress of smoking, an effect more pronounced among heavy and long-time smokers [248]. These interacting effects of smoking and nutrition are further compounded by their association with other indicators of low SES such as low education and income contributing to allostatic load [139,251]. Nutrient intake may be ameliorative after an insult has occurred as shown in rat models of fetal alcohol syndrome where an omega-3 fatty acid enriched diet reversed the cellular effects of prenatal ethanol exposure on the fetal brain [222]. Therefore with respect to policy interventions, nutrition in the form of improved food security and micronutrient intake may serve to counteract the negative influences of both low SES and air pollution exposure [252–257].

The complex mixture of particulate air pollution, especially $PM_{2.5}$ and UFPs which includes absorbed PAHs and various metals, also emerges as an important target for risk reduction and management. The deserved scrutiny stems from the ubiquity in the environment, the myriad of emission sources and their established association with APOs [88,98,258]. The ubiquity of $PM_{2.5}$ and UFPs in the environment means that a high proportion of people are exposed resulting in a high etiological fraction. Therefore, even a

modest reduction in exposure will have a large population effect with reduction of the societal costs of APOs [259]. Notably, their sources are primarily local, such as vehicle emissions and industrial land-use. This makes them modifiable risk factors that can be addressed at the municipal and provincial/state level with better urban planning to reduce vehicle traffic, increasing access to green-space and enforcing air quality regulations [260–263].

Not unlike the accumulation of evidence on smoking and health outcomes or that of air pollution on cardiovascular and pulmonary health [264], the epidemiological and toxicological research over the past two decades has established a consistent dose-response association with high biological specificity, temporality and plausibility [3,55,177]. Taken in concert, these characteristics and further corroborating research should lend strength for evidence-based policy for intervention strategies targeting high risk areas in order to reduce the environmental burden of disease attributed to particulate air pollution [98,265,266].

6.0 Conclusion

Adverse pregnancy outcomes such as fetal growth restriction and preterm birth are a public health priority of global importance. We have brought together the multidisciplinary literature on the current state of evidence linking the physical and social environment to specific adverse pregnancy outcomes. The evidence suggests that various exposures, whether socially or environmentally determined, may be interpreted by the fetoplacental unit in similar ways resulting in a common pathological set-up for adverse outcomes, namely deficient deep placentation. Given this background, well planned future epidemiology studies using multilevel models exploring various biological effects of the social and physical environment will have the potential to provide the evidence to establish crucial windows of fetal vulnerability with an aim to identify and mitigate modifiable risk factors.

7.0 Endnotes

1- Implantation of the blastocyst (0.1 mm in size) begins on day six following conception in which it completely embeds itself within the maternal uterine endometrium, usually on the upper posterior (fundal) wall. The peri-implantation period (approx. day 1-20 post-fertilization) is arguably most critical period of reproduction as two-thirds of conceptions fail at this time, often unbeknownst to the individual [72]. Individual variability in genetic predisposition interacts with both environmental (exogenous)

and maternal (endogenous) stress exposures that can lead to defective placentation with subsequent obstetrical complications and/or the development of birth defects via teratogenesis [71,72,245]. Indeed, fifty percent of confirmed miscarriages (pregnancy loss prior to 20 weeks gestation) are due to abnormal embryonic karyotype (chromosomes), a natural biosensor mechanism to recognize and eliminate defective embryos [267]. Furthermore, ectopic pregnancies (implantation anywhere other than uterine cavity) and placenta previa (implantation on the lower inferior segment of the uterus near the cervix) are risk factors of maternal mortality or morbidity and are often either terminated or delivered preterm via caesarean birth respectively [268].

Successful implantation and subsequent placentation involves the coordinated differentiation of the trophoblast (outer cell layer of the blastocyst) into three distinct cell populations, syncytiotrophoblasts (STBs), cytotrophoblasts (CTBs), and extravillious cytotrophoblasts (ECTBs) [68,217]. The STB is the main endocrine hormone synthesis component of the placenta and rapidly expands into the maternal endometrium. The CTBs are the mitotically active progenitor (stem) cells which migrate in-behind the expanding mass of the STB which eventually gives rise to the basal plate of the definitive discoid placenta around mid-gestation. Finally, the ECTB are subsequently differentiated from the advancing CTB cells beyond the basal plate to infiltrate the underlying maternal decidual cells and uterine spiral arteries. At the end of the third week of gestation the definitive elements of the discoid placenta are in place: the chorionic plate from which the villi arise and fetal blood will flow, a basal plate in which anchoring villi are attached, and lacunar (intervillous) spaces into which maternal blood will circulate (Figure 5) [217]. The histological structure of the human placenta is commonly described as hemochorial in which the fetal/embryonic tissues are in direct contact with maternal blood.

The free flow of oxygenated maternal blood into the placenta along with antioxidant enzymes (SOD - superoxide dismutase, catalase and GPx - glutathione peroxidise) serves a physiological role facilitating maternal-fetal nutrient transfer and gas exchange; however the consequential burst of ROS may negatively impact on-going placental differentiation and growth, such as shallow trophoblast invasion of maternal spiral arteries, if antioxidant defences are depleted (Figure 6) [68,192].

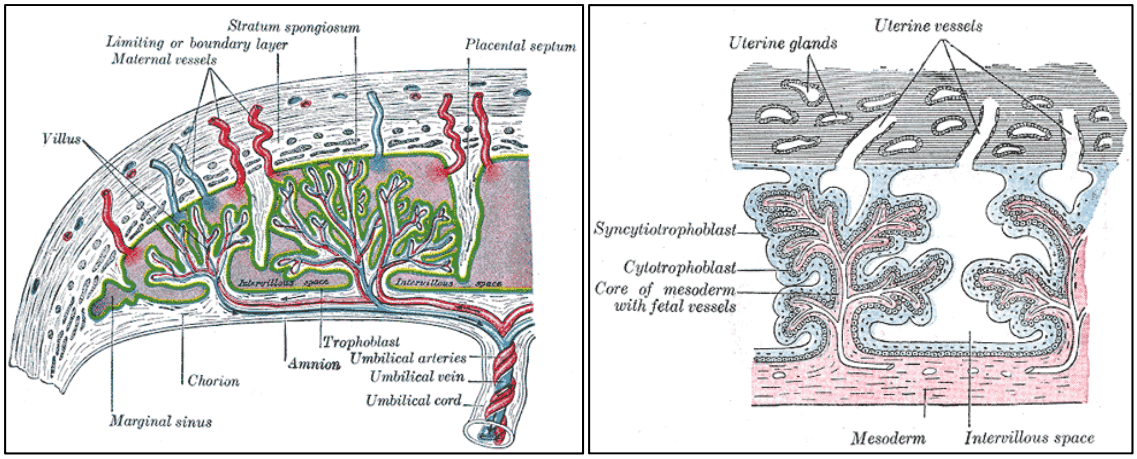

Figure 5: Scheme of placental circulation and features (Grey's Anatomy lithographs)

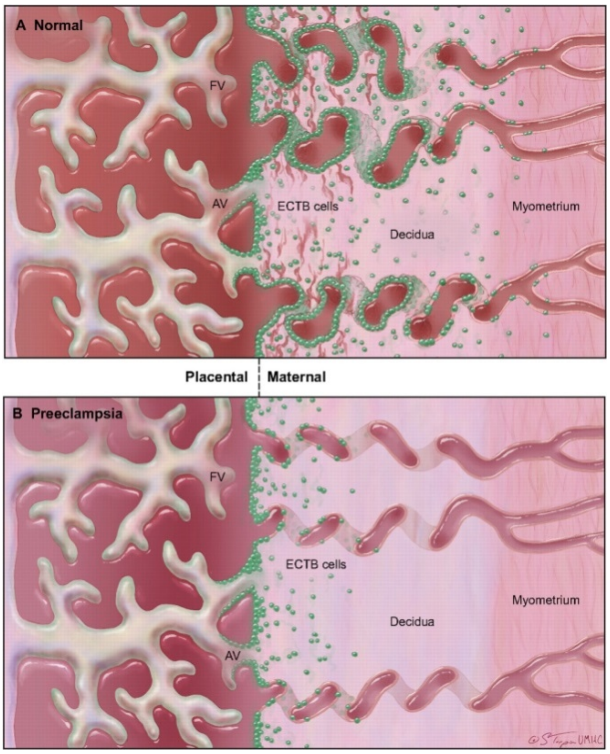

Figure 6: Invasion defects in preeclampsia

(A) Normal Placenta:
The extravillous cytotrophoblast (ECTB) cells (green) migrate into the decidua of the maternal endometrium where they enter and remodel the maternal spiral arteries from an endothelial cell type to endovascular ECTB (eECTB) cells losing their responsiveness to endogenous vasoactive compounds and maximizing blood flow into placental intravillious spaces.

(B) Preeclamptic Placenta:
The ECTB invasion into the decidua is shallow and limited, with many ECTB cells in the basal plate remaining attached to anchoring villi (AV). Endovascular invasion and remodelling of the spiral arteries is absent or reduced, thus constricting blood flow and reactive to maternal stimulus such as stress and other vasoconstricting agents. FV: floating villi. [269]. Image courtesy of The Curators of the University of Missouri (2011).

2- Deficient deep placentation is thought to result in reduced and intermittent placental perfusion thereby restricting blood flow and limiting oxygen and nutrient supply to the fetus. The maternal adaptive response is to increase blood pressure to compensate for the restricted flow. The ensuing placental hypoxia in the latter two trimesters leads to the upregulated expression and secretion of soluble antiangiogenic factors (sFlt1 and sEng) which antagonize proangiogenic factors (VEGF, PlGF, and TGF-β1) causing systemic endothelial dysfunction characteristic of PIH/PE [115].

3- The placenta is a multi-functional organ and is responsible for three major roles at the maternal-fetal interface. First, the placenta is an immunologic barrier between mother and fetus, and is thought that the placental trophoblast and maternal immune system positively interact for the success of the pregnancy [44,173,217]. The syncytiotrophoblast acts through the production of various cytokines and chemokines responsible for the coordination, migration, differentiation, and function of the maternal immune cells [182,183]. This is achieved through a non-linear series of positive and negative feedback pathways with the stimulation and suppression of molecules with both pro- and anti-immunosuppressant properties (interleukins, integrins and glcyodelin – see Table 1). Interference with the production or secretion of these substances may result in the impaired maternal immune response to the semi-alliograph fetal-placental unit leading to several APOs including early pregnancy loss, PIH/PE, and PPROM [61,134,175,185,186].

The second major function of the placenta is its synthesis of steroid and protein hormones vital in the progression of the pregnancy (Table 1). Most of the circulating substances in Table 1 appear to be synthesized by the syncytiotrophoblast. Interference with the production or secretion of these substances by xenobiotics(e.g. cadmium, lead, arsenic) may result in several APOs, such as early pregnancy loss, PIH/PE, impaired immunoprotection and PPROM[134,175,185,186,236]. For example, the PM-mediated oxidation of low-density lipoproteins (LDL) may interrupt a cascade of events necessary for the fetal production and export of oestriol, quantitatively the most significant oestrogen in maternal circulation in late pregnancy[97,217]. Chronic or acute maternal psychosocial stress also has the potential to disturb immune and endocrine signalling pathways via the hypothalamic-pituitary adrenal (HPA) axis [47,72,136,138].

The third major function of the placenta involves various transfer mechanisms similar to those found in other epithelial systems. The major transfer mechanisms include: simple diffusion of lipophilic substances (e.g. oxygen, CO2, fatty acids, steroids, fat soluble vitamins, anesthetic gases), restricted diffusion of hydrophilic substances, facilitated diffusion via a membrane bound carrier(e.g. glucose and other carbohydrates), active transport which requires energy (e.g. amino acids, iron, calcium, and other divalent cations), receptor-mediated endocytosis and exit mechanisms [45,217]. Regulation of placental nutrient transport is controlled by several different

endogenous mechanism, including imprinted genes, placental signaling pathways, various cytokines and hormones such as insulin, leptin, glucocorticoids and oestrogens (for review see [45]). Many of the above listed factors can be indirectly affected by exogenous mediators (e.g. PM and PAH exposure, stress). However, exogenous mechanisms with direct modes of action on nutrient transport include cadmium (Cd), lead (Pb) and oxidative stress. For example, Cd exposure from tobacco smoke, air pollution and/or diet readily interferes with the active transport of essential minerals to the fetus, particularly zinc and calcium [46,135,196,226,227]. Cd and Pb exposure has been shown to reduce glycogen concentrations thereby potentially limiting available glucose to the fetus [229], and oxidative stress negatively affects the placental transport of amino acids as well as glucose [45].

Table 1: Biological factors involved in pregnancy, their role and up/down-regulation

Name	Function and Role	up/down-regulation	Ref.
Progesterone, oestriol (E_3), oestrone (E_1), 17β-estradiol (E_2)	-Steroid hormones, regulate menstrual cycle, prepares endometrium for implantation. -Biosynthesized by placenta using LDL cholesterol in maternal blood -Up-regulates many other items below	↓ by Cd, other heavy metals ↓ by PM via oxidized LDL cholesterol ↑ E2 metabolism to reactive metabolites via PAH-induced CYP450	[75,216,229,270]
Human Chorionic Gonadotrophin (hCG)	-Glycoprotein Hormone -Released by blastocyst, initial pregnancy recognition and corpus luteum survival -Detectable by week 3, peaks week 11 -Stimulates initial progesterone release -Immune tolerance, trophoblast differentiation and angiogenesis	↓ by Cd exposure, indirectly via reduction of leptin ↓ in chorioamnionitis ↑ uNK cell proliferation ↑ by GM-CSF ↑ by IL-1β, TNF-α via IL-6 ↑ LIF, VEGF, MMP-9	[49,182,186,216,271]
Granulocyte macrophage-colony stimulating factor (GM-CSF)	-Cytokine -Promotes DNA proliferation, differentiation and placental secretory activity -Required for optimal placental development, fetal growth and survival	-Synthesis in uterine epithelial cells is regulated by estrogen -Low blood concentration levels in women with recurring miscarriages	[271,272]
Placental and Vascular Endothelial Growth Factor (PlGF, VEGF)	-Pro-angiogenic growth factors for vascular development of embryo, placenta and spiral artery remodelling -Promotes vasodilation -Low PlGF:sFlt ratio in preeclampsia	↑ by hCG, hypoxia in early pregnancy ↓ by sFlt and sEng via excess oxidative stress/inflammation	[63,194]
Interleukin (IL), Tumour Necrosis Factor (TNF), & Leukemia Inhibitory Factor (LIF)	-Large family of pro/anti-inflammatory cytokines (non-enzymic cell messenger) -Involved in all aspects of pregnancy -Pro-inflammatory: IL-1α/β, IL-6, TNF-α -Anti-inflammatory: IL-10, IL-4 -LIF essential for implantation, released by uNK, regulate invading pTBCs	↓ IL-6 by hCG, progesterone ↑ IL-6 by exercise ↑ LIF by hCG & IL-1β ↑↓ by heavy metals	[174,175,182,183,272]
Prostaglandins ($PG-E_2$)	-Increase vascular permeability in the decidua and at implantation site. -Stimulates contractions, labour onset -Regulated by COX-2	↑ by IL-6, IL-1β, TNF-α ↑ by infections ↓ by dietary phytophenols	[129,273]
Glycodelin-A, Galectins	-Early secretion by uNK cells modulates endometrial immune adaptation	↑ by hCG, progesterone ↓ by stress	157,158,162]
Integrins	-Cell surface receptor and adhesion molecules, important in EVT invasion of decidua and ECM remodelling	↑ by IL-6 and VEGF Altered by Cd	[63,185,193]
Glucocorticoid Steroids (GS) e.g. cortisol & corticosterone	-Upregulated with HPA-axis activation -Involved in implantation, fetal-placental growth, organ development, utero-placental adherence, onset of parturition -Excess is detrimental, fetal exposure regulated by placental 11β-HSD2	Hormonally regulated ↑ $PG-E_2$, hCG ↑ with blood Pb, life stress ↑ by IL-1β, IL-6 ↓ uNK cells ↓ 11β-HSD2 by Cd, hypoxia	[29,136,182,236]

Acronyms used: 11β-HSD2: 11β-hydroxysteroid dehydrogenase type 2; Cd: Cadmium; COX-2: cyclo-oxygenase-2; CYP450: cytochrome P450; ECM: extracellular matrix; EVT: extravilloustrophoblasts; HPA: hypothalamus-pituitary-adrenal; LDL: low-density lipoprotein; MMP: matrix metalloproteinase; Pb: Lead; sEng: soluble endoglin; sFlt: soluble fms-like tyrosine kinase; pTBC: placental trophoblast cells; uNK: uterine natural killer.

4- Crosstalk from AhR to other signalling pathways in the fetal-placental unit includes PAH-induced AhR interacting with the hypoxia-inducible factor (HIF) which, depending on the timing of exposure, may alter oxygen tension in early pregnancy and result in miscarriage or subsequently reduced trophoblast invasion leading to PIH/PE and/or IUGR [75]. Moreover, depending on the source mixture, PAHs are capable of inhibiting their own metabolism into harmful metabolites which may explain the discrepancies in laboratory testing of single PAH chemicals versus whole mixtures [75]. Similarly, the differential AhR induction between CYP1A1 and CYP1B1 dictates metabolite toxicity. For example, estradiol metabolism by CYP1B1 converts 17β-estradiol (E_2) to carcinogenic 4-hydroxyestradiol (4-OH E_2) which forms DNA-adducts and generates ROS. In contrast, CYP1A1 converts E_2 into non-carcinogenic 2-hydroxyestradiol (2-OH E_2) which is shown to be markedly stimulated in placentas of smokers via the up-regulation of CYP1A1.

Increased CYP1A1 levels are significantly increased in ex-smokers compared to those who never smoked. PAHs are lipophilic and tend to be stored in the kidneys, liver, and to a lesser degree the spleen, adrenal glands and ovaries. Thus PAHs may be re-released into the blood circulation during pregnancy, similar to the mobilization of lead from maternal bone stores pre and postpartum, [75,274]. Toxic PAH-DNA adducts from smoking are detectable in ovarian granulosa-lutein cells, oocytes and spermatozoa. Paternal transmission of altered DNA to preimplantation embryos were shown in assisted contraception experiments and may compromise embryonic development such as failed implantation or early pregnancy loss [275]. Therefore perhaps the increased rates of infertility and other risks associated with older maternal age has less to do with biological decline and more to do with increased toxic body burdens in both men and women. Exposures typical of urban air pollution and moderate pre-conception maternal smoking have shown to adversely affect placental morphology in mice models [276,277].

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Chapter 2: Methodological Background

"the major causes of disease and suffering in the population are firmly rooted in the behavioural, social, and psychological worlds in which people live… [and] are embedded in multiple environmental, geographical, institutional, and economic contexts." - Kaplan, G.A. Research Lecture at the Nobel Forum, April 8, 1999, p.2 [1].

1.0 Introduction

While the roots of a social approach to health could arguably be traced back to the sanitary campaigns of the 19th century in Britain, the focus was primarily on improving environmental hygiene to prevent transmission of pathogenetic diseases typical of non-industrialized states. It was the Whitehall study with a Lancet paper in 1978 that definitively established the epidemiological association between chronic disease status and social class in a modern industrialized setting [3]. By following a prospective cohort of 17,530 civil servants in London for seven years, it showed that risk factors for coronary heart disease (CHD) including smoking, leisure exercise, plasma cholesterol, blood pressure, height and weight only partially explained occupational class differences in CHD mortality [3].

Around the same time, John Cassel proposed in a 1976 lecture series paper that psychosocial stress within the context of the larger social environment is capable of altering disease resistance of the host to the ubiquitous microbiologic and physiochemical agents in the environment [4]. Cassel advanced the concepts of several scientists, notably Rene Dubos for his 1965 book *Man Adapting* and L.E. Hinkle for his 1973 paper *The Concept of Stress in the Biological and Social Sciences*, from which he quotes "It is evident that any disease process, and in fact any process within the living organism, might be influenced by the reaction of the individual to his social environment or to other people" [4][p. 3]. He goes on to argue that the psychosocial process or stressor is unlikely to have a direct pathology with etiologic specificity or a dose-response relationship for any given disease; but rather that these processes can in part contribute to all disease indirectly via altered neuroendocrine imbalance [4]. Forty years later, research is just now starting to elucidate the possible mechanisms [5,6].

With respect to the Whitehall study, the clear mortality gradients by subtle differences in social position within white-collar occupations was ground breaking and in part led to what is now termed as *the social determinants of health*. Repeated twenty years later with a new cohort (the Whitehall II study), the results were substantiated which showed no diminution in social class differences in morbidity [7].

The following section will discuss two principle issues in observational epidemiology 1) the assessment socio-economic status (SES), what it is and how to measure it; and 2) consideration of health outcome data, specifically perinatal health data and the data contained in the BC Perinatal Database Registry (BCPDR). The subsequent section then shifts to exposure assessment, specifically scenario-based land use regression models, and their use within the context of population-based epidemiologic research such as this dissertation.

2.0 Socio-economic Status Background

Socio-economic status (SES), or socio-economic position, is an umbrella term generally used to measure social inequity. There are several variables often used as indicators of SES, the most common being income, occupation and/or educational attainment measured at both the individual and population level [8–11]. The indirect mechanisms by which SES variables operate to affect individual and population health are not fully understood despite the long history of research supporting the association [12–16]. It is important to recognize that the causal pathways of SES operate at multiple levels of hierarchy (individual, household, neighbourhood, city, etc.). So called 'upstream' determinants (income inequality, impoverished communities) lead to 'downstream' determinants or mediating exposures (unhealthy behaviours, allostatic load) that exist in relation to one another to influence disease risk as opposed to being independently acting phenomena [17]. For example, a person's food choice is influenced by the availability and accessibility of healthy food (or lack thereof) in the neighbourhood or community, the consumption of which in turn reinforces its availability in stores, creating a positive feedback loop [18,19]. Further, a person's behaviour is influenced by the prevalence of that behaviour among their peers [20] which then normalizes that behaviour within the social environment with potential for intergenerational transmission [21]. These two examples represent two different types of determination, reciprocal causation and structural causation respectively [22], and may subvert attempts to disentangle the individual (compositional) factors from the social (contextual) factors unless careful effort to model these hierarchical phenomena is undertaken [23–26].

2.1 Measuring Socio-economic Status

When planning the conceptual model it is imperative to consider not only the level of measurement (compositional, contextual), but also the manner in which SES is measured

(absolute or relative), its presumed role in the model (confounder or risk factor), and how/if it will be adjusted for [10]. The three main indicators of SES (income, education, and occupation) are interrelated but are not necessarily interchangeable, and using one measure over another may affect the results and mislead interpretations [27–30]. Guidance on selecting a measure of SES can be vetted using nine criteria provided by Liberatos et al. (1988). They include: conceptual relevance (relative status or absolute class ranking), its role in relation to other risk factors and the outcome, its applicability to the study population, its time relevance and stability, its reliability and validity, whether or not there are multiple versus single indicators, discrete versus continuous measures, its simplicity, and its comparability with other studies [10].

Inequities in APOs across racial/ethnic minority status often parallel SES disparities. This has been observed in many multiracial countries, with evidence to suggest both confounding and effect modification. Black-White differences in PTB risk persist after adjustment for SES differences [17]. Similarly, in Canada Aboriginal status correlates with many unique upstream determinants of low SES given the colonial history which results in a disproportionate incidence of APOs after adjustment of SES differences [31–37]. However, low SES remains associated with APOs even within racial/ethnic populations and warrants further investigation into possible effect modification by neighbourhood-level factors [17, 30]. For example, the 'healthy migrant paradox' in Montreal, Quebec was found to depend on the country of origin, their level of education and various neighbourhood factors [38].

Alternatively, true biological and genetic differences may partly account for the observed discrepancies; and the potential for misclassification of newborns as either normal, SGA or large-for-gestational age (LGA) may have implications on interpreting risk rates [39]. For example, First Nations births in British Columbia (BC) tend to have significantly higher median and mean birth weights at all gestations compared to all births in BC despite having lower SES values in general [40]. Conversely, infants of Chinese and South Asian descent born in BC and elsewhere have significantly lower birth weights than infants of European descent [39,41]. Using the standard provincial birth weight chart for newborn classification, less than ten percent of First Nations infants would be considered SGA-10 resulting in false-negatives and the potential neglect of health risks faced by small babies misclassified as normal growth. The adoption of ethno-specific or customized fetal growth charts may be warranted in order to prevent the potential misclassification of newborns as SGA or LGA [42]; however, the benefits of customized birth charts continue to

be debated [43–45]. The use of a smaller cut-point, such as the 3rd or 5th percentile for birth weight would reduce the risk of false-positive by capturing truly growth compromised newborns.

In perinatal epidemiology, the use of maternal education as an indicator of SES has been shown to be stronger than, and independent of, neighbourhood income in relation to APOs [46]. Both individual-level and area-based measures of maternal education are strong predictors of APOs, regardless of whether education was evaluated as a relative or absolute inequality measure [47]. Maternal education is an upstream determinant that predicts many downstream exposures associated with APOs, including heavy smoking, drug use, low level of prenatal care, stressful work, infections and psychosocial factors [17]. Low education and neighbourhood SES have been associated with nutritionally poor foods choices and suboptimal fruit and vegetable intake [19].

2.2 Contextual (population-level) Measures of SES

Facilitated by developments in statistical software programming and advances in computing speed, the popularization of multilevel models over the past two decades has spawned a resurgence of interest in the analysis of population-level measures of SES on health [11,48,49]. Of particular interest is the ability to estimate coefficients of the (cross-level) interactions between level-one predictors of the individual and level-two predictors measured at the group level [23,50,51]. The common terminology used synonymously with 'contextual' includes neighbourhood, group, level-2, and area-based. Level-2 variables can represent geographic hierarchies, such as neighbourhoods, cities, watersheds, but can also represent time points such as in longitudinal studies, class rooms, schools, or any grouping or clustering variable. Hierarchical multilevel models are reviewed in more detail in the following section.

There are several ways to create or obtain group level measures, national census being the most common data source. Similar to individual level measures, the most frequently used are income and education, often represented by the group mean. The percentage of unemployed is a common occupational measure used. Compositional indices based on the statistical weighting of several indicator variables have been regularly used as they can incorporate the multiple dimensions of SES in a neighbourhood [10]. The concept of material deprivation refers to the ability to access material goods and conveniences, while social deprivation reflects the degree of family-community cohesion and social interactions. With the aid of geographical information systems, area-based deprivation

indices have become a common tool to assess patterns and degree of SES inequalities in relation to health [52,53]. In this dissertation, I use an SES index produced by Chan et al. specifically for the study of health outcomes related to environmental pollution [54]. This index reflects more dimensions of SES than the deprivation index produced by Pampalon et al. [22] by using 22 SES census variables including cultural identities and housing characteristics, and was shown to perform better in capturing gradients in prevalence of pregnancy outcomes. It also had more complete spatial coverage compared to the Pampalon index, greatly reducing the number of imputed values for rural census DAs.

Indicators used to construct a deprivation index should be associated with health, be related to SES, and be ascertainable by some standardized geographic census area. It is possible to create group-level variables using individual-level indicators of SES such as education. This could be average years of education for a defined neighbourhood or the percent of the population without a high school diploma. Issues regarding potential "same source bias" are generally the result of poor data quality and/or high number missing values. A recent study comparing individual-level derived maternal neighbourhood education and a census-based measure of education found that potential bias was minimal yielding similar associations with PTB [47].

One area-based measure that confounds and interacts with measures of SES is rural location. There is no absolute definition of rural other than being 'not urban', but this dichotomization can mask underlying trends in perinatal health [55–59]. Definitions of rural are often based on population size and dynamics and the interrelationship of residents between other locations, particularly larger cities and metropolitan areas. Commuter flows and "metropolitan influenced zones" have been developed to classify rural in relation to the nearest urban center on a continuous scale using hierarchical-related census geographic areas (i.e. the rural-urban continuum) [60,61]. In this dissertation I use Statistics Canada's Metropolitan Influence Zone (MIZ) method described above to define rural residence into a dichotomous (Census Metropolitan Areas (CMA) and Census Agglomeration (CA) areas versus Census Subdivisions (CSDs) that lie outside these areas) as well as a five value categorical variable ranging from CMA/CA to the four zones of influence (strong, moderate, weak, and none) according to the degree of influence that CMA/CAs have on them [60].

Finally, when creating group-level SES indicators based on a geographic boundary, how that boundary is defined may influence the results obtained. As stated above, administrative census boundaries are the most common for several reasons. The data is

routinely collected with a high degree of quality and is fairly stable over time. However, researchers have implemented techniques to create new boundaries with a high degree of within-area homogeneity thereby reducing the potential for within-area confounding [62,65,66]. In Canada, while DAs do not necessarily represent existing neighbourhood communities [62], they can serve as adequate proxies for a general catchment area of personal home-life activities [63,64].

Underlying the boundary selection issue is the concept of spatial scale dependencies or the 'modifiable areal unit problem' (MAUP) [67]. MAUP has two distinct components: the scale effect and the zoning effect. The scale effect recognizes that as one aggregates data up the spatial hierarchy the relationship between variables can change often strengthening the regression relationship but reducing statistical power due to there being fewer units in the analysis. The zoning effect refers to the actual delineation of boundaries and how their manipulation can drastically alter neighbourhood characteristics due to the inclusion or exclusion of certain data points (i.e. people or disease events). Consideration of the spatial unit used in the analysis should be based on the research question and the process that is attempting to be modelled. In this dissertation we use census DAs as the neighbourhood-level unit of analysis. DAs are the smallest geographical unit for which census data are available and represent neighbourhood blocks ranging between 200–800 people. The DA was chosen partly due to convenience in that it was the spatial unit that matched the SES index as well as the other SES census data such as education and immigrant density. But the DA was also chosen for practical reasons due to the scale of this project encompassing the entire province of BC. While scaling up in urban areas could have been explored, this would be impractical for the larger geographic sizes of rural DAs. Managing three different geographic spatial units or having different spatial units for urban and rural areas would be an additional complication with possibly minimal benefit in interpretation. Furthermore, using DAs allows for the comparison of results to other studies.

3.0 Multilevel Models & Analysis

** much of this section has been adapted from Snijders and Boskar, Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling [25].*

Multilevel models go by many names and have several flavours. While not a new methodology, it is only in the last two decades that their emergence has moved beyond the social sciences (sociology, education, economics, criminology, etc.) and into population health and epidemiology. Multilevel analysis is a methodology for data with nested sources

of variability, wherein the between group (or cluster) variability is as important a research question as the within group variability. By decomposing the overall variability into '*within*' and '*between*' units of analysis, the researcher is able to adjust for and quantify *intra*-group dependence while simultaneously quantifying the *inter*-group variability [25]. For example in educational research, there can be variability measured at the student level with individual attributes (e.g. IQ on test scores). These students are nested within schools that have their own characteristics and it is possible to measure the between-school variability across different schools (i.e. each school will impart some unique effect on individual test scores and the addition of school-level variables (e.g. public vs. private) are used to help explain the measured differences). Additionally, schools are often nested within school districts with distinct characteristics. Depending on the research question, all three of these 'levels' (student- school-district) may have interesting and necessary variability to account for.

Multilevel analysis as it is today was formed by the convergence of two distinct fields of inquiry; namely contextual analysis as a development in the social sciences recognizing the influence of social context on individual behaviour/outcomes, and the development of mixed effect statistical methods that allow nested regression-type model coefficients to be either fixed or random. The confluence of these two streams coincided with the emergence of the computational processing era in the early 1980s which allowed greater accessibility in running more complicated models [25].

The hierarchical linear model is the backbone of multilevel analysis and is essentially an extension of multiple linear regression to include nested random effects [25]. The employment of a nested research design sometimes arises from necessity and other times as curiosity. Respectfully, this can be referred to as *dependence as a nuisance* or *dependence as an interesting phenomenon*. The former arises from multi-staged sampling designs which inherently lead to dependent observations (i.e. selection of a grouping unit (school) increases the likelihood in the selection of the individual unit (student)). This dependence in sampling violates an essential assumption of inferential statistics causing deflated standard errors and potentially leading to Type I errors. In the latter situation, dependence between and within nesting structures is the focal interest where one wishes to make inference at both levels. Regardless of the motivation, single-level statistical models are no longer valid although there are statistical means to deal with nuisance clustering of observations (e.g. sandwich estimators of standard errors) [25].

The terminology used to describe the multilevel model is varied. For our purposes here, we will refer to the macro-units as level-2 or group-level units and signified in equations as a subscript *j*. The micro-units will refer to level-1 or individual-level units and signified in equations as a subscript *i*. In the study of multilevel systems, six propositions can be distinguished and are diagramed below in Figure 7 to facilitate comprehension.

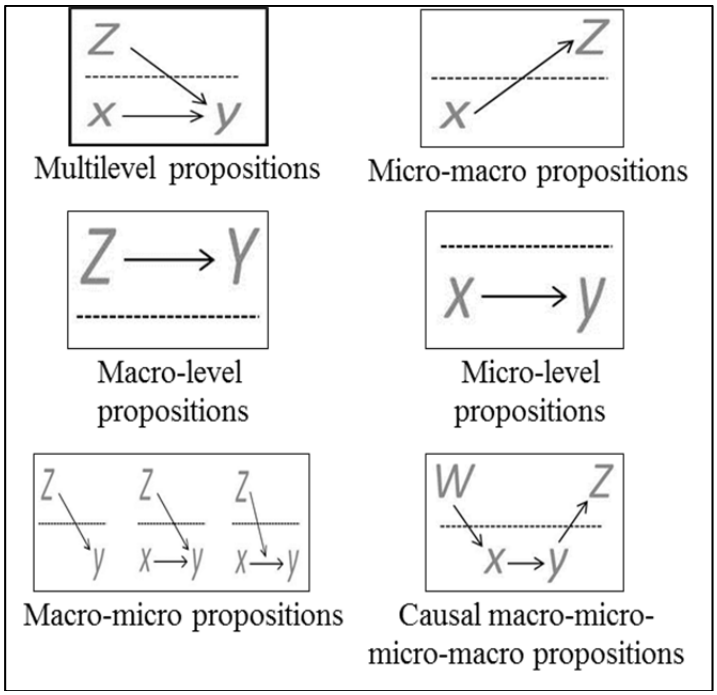

Figure 7: Six theoretical multilevel proposition

3.1 Random Intercept Model

The random intercept model is one in which the intercept is allowed to vary randomly between the level-2 groups. This allows for each level-2 group (e.g. neighbourhoods, schools) to have its own intercept along with its variance from the overall (global) intercept. When regular (ordinary least squares or OLS) regression is used on data that has a meaningful hierarchical structure, it is (erroneously) assumed that all the group structure is represented by the explanatory variables which is reflected by the single fixed intercept. Therefore, for any two individuals it is inconsequential whether they are from the same or different school or neighbourhood.

The simplest way to think about random intercept models, or hierarchical linear models in general, is to consider it a special case of regression models but with more than one error term. The group-dependent intercept can be split into an average intercept and the group-dependent deviation from the overall mean (i.e. level-2 random error). This

signifies the realization that some groups will have higher responses *Y* on average and others will have lower responses. The regression equation below (Eq.1) shows that the intercept depends on the group (signified by the subscript *j*). For now the β_1 coefficient of *X* is constant or fixed, but the next section describes how it too can be allowed to vary between groups to produce the random slope model.

(Eq.1) $Y_{ij} = \beta_{0j} + \beta_1 x_{ij} + R_{ij}$

(Eq.2) $\beta_{0j} = \gamma_{00} + U_{0j}$

(Eq.3) $Y_{ij} = \gamma_{00} + \gamma_{10} x_{ij} + U_{0j} + R_{ij}$

Referring to Eq.1, the intercept from level-1, β_{0j}, is estimated as a model parameter with its own group-level regression coefficient (γ_{10}) and error term (U_{0j}) that deviates from the overall average intercept (γ_{00}). Substitution produces the random intercept model presented as Eq.3, sometimes referred to as an 'intercept-as-coefficient model'.

The *empty* or *null* model is a model that does not contain any explanatory variables. Here, the dependent variable (Y_{ij}) is only a function of the overall mean (γ_{00}), the group-level random effect (U_{0j}), and the individual-level random effect (R_{ij}).

(Eq.4) $Y_{ij} = \gamma_{00} + U_{0j} + R_{ij}$

It is assumed that the random variables U_{0j} and R_{ij} have a mean of 0, are mutually independent, drawn from normally distributed populations, and have variance var(R_{ij}) = σ^2 and var(U_{0j}) = τ_0^2. The null model provides the basis for calculating the *intraclass correlation coefficient* (ICC), a parameter that indicates how the variability in the data is partitioned between the two levels. The ICC is zero when there is no *between-cluster* (macro-unit) variance, and increases when the *between-cluster* variance increases relative to the *within-cluster* variance. Represented by the Greek symbol rho (ρ), the ICC is calculated by dividing the *between* population variance of the macro-units by the sum of the macro- and micro-unit variance, $\tau^2/(\tau^2 + \sigma^2)$. The ICC can be interpreted in two ways: 1) it is a measure of the correlation between two randomly drawn micro-units belonging to the same macro-unit drawn at random; 2) it is the proportion of variance accounted for by the group-level.

From the null model we begin to introduce explanatory variables in order to explain the variability of *Y* at both level-1 and level-2. Returning to Eq.3, this model has four

parameters: the two regression coefficients γ_{00} and γ_{10} which make up the fixed effects and the two variance components σ^2 and τ_0^2 (the random effects). The values U_{0j} are the main group-level effects (or group residuals) that are left unexplained by *X*. The overall intercept γ_{00} is the fixed intercept for the average group (averaged over all groups but with larger groups having more influence on its estimation than small groups). The fixed regression coefficient γ_{10} is interpreted in the usual way (i.e. a one-unit increase in *X* is associated with an average increase in *Y* of γ_{10} units).

The addition of level-2 explanatory variables, denoted by $Z_1 \ldots Z_q$, takes the form in one of two ways. Level-2 variables can be directly defined by a unit characteristic (e.g. the level-2 group of schools can be either private or public). Alternatively, a level-2 variable can be defined by the aggregated units at level-1 (e.g. the mean SES of students in a school). This latter characterization based on group means is a particularly important type of explanatory variable as it allows for the differentiation between *within-group* and *between-group* regressions to be expressed. The within-group regression coefficient expresses the expected difference in *Y* between cases within the same group for a one-unit difference in the explanatory variable *X*; whereas the between-group regression coefficient is the expected difference in the group means on *Y* between groups for a one-unit difference in their mean values of *X*. This is noteworthy because the processes at work within groups can differ from the processes at work between groups, and could therefore have vastly different conceptual interpretations. For example, the effect of a high proportion of neighbourhood-level maternal smoking on birth weight has a different conceptual interpretation than that of individual-level maternal smoking on birth weight.

3.2 Random Slope Model

In addition to groups differing with respect to the average value of the dependent variable (i.e. random between-group intercept variance), it is possible for the effect of an explanatory variable to also differ between groups (i.e. random between-group slope variance). This is referred to as *heterogeneity of regressions across groups* or as *group-by-covariate interaction* in the analysis of covariance (ANCOVA) terminology. Returning to Eq.1, a model with group-specific regressions of *Y* on a level-1 variable *X*, both the intercept β_{0j} and the regression coefficients, or slopes, β_{1j} can be split into an average coefficient and the group-dependent deviation to produce Eq.2 (as seen above in the random intercept model) as well as Eq.5. Substitution leads to the model in Eq.6

(Eq.1) $Y_{ij} = \beta_{0j} + \beta_1 x_{ij} + R_{ij}$

(Eq.2) $\beta_{0j} = \gamma_{00} + U_{0j}$

(Eq.5) $\beta_{1j} = \gamma_{10} + U_{1j}$

(Eq.6) $Y_{ij} = \gamma_{00} + \gamma_{10} x_{ij} + U_{0j} + U_{1j} x_{ij} + R_{ij}$

Again here, $\gamma_{00}$is the overall average intercept and γ_{10} is the overall average regression coefficient and are referred to as the fixed effects. The level-2 residuals, U_{0j} and U_{1j}, along with the level-1 residual R_{ij} are referred to as random effects and are assumed to have a mean of 0 given the values of the explanatory variable *X*. The term $U_{1j} x_{ij}$ is regarded as a random interaction between group and *X*; that is, the effect of a level-1 attribute can differ between groups. The random intercept and random slope are considered latent variables, as they are not directly observed but are influential in producing the observed variables. The terminology is that *X* has a random slope, or a random coefficient, or a random effect. The random intercept and slope are often correlated; however, model assumptions presume them to be independent and identically distributed between groups and that they are independent of the level-1 residual R_{ij}. Also, it is assumed that all R_{ij} are independent and identically distributed. The variance and covariances of the level-2 residuals are denoted as:

$\text{var}(U_{0j}) = \tau_{00} = \tau_0^2$

$\text{var}(U_{1j})\ \tau_{11} = \tau_1^2$

$\text{cov}(U_{0j}, U_{1j}) = \tau_{01}$

The random slope model implies heteroscedasticity (unequal variance) in that the correlation of individuals within the same group as well as the variance of *Y* is dependent on the value of *X*. For example, students from low SES households may benefit much more from a well-resourced school compared to students from high SES households. Therefore the school adds a component of variance, but primarily for the low SES students indicating how the variance depends on the value of *X* for student-level SES.

3.3 Inclusion of Level-2 Variables and Cross-Level Interactions

The aim of regression analysis is to explain variability in the dependent variable. For multilevel regression, there is not only variability between individuals (level-1 residual,R_{ij})

but also variability between groups to which the individuals belong (level-2 random intercept, U_{0j}) and variability between groups in how they influence/interact with individual-level attributes (level-2 random slope, U_{1j}). Each represent different parts of the unexplained variability, and thus each can be the point of focus when considering explanatory variables. The addition of individual, or level-1, variables aim to reduce the level-1 residual variance (σ^2). Their inclusion may also reduce the residual variance at level-2 given that groups can differ with respect to their composition of level-1 variables. The addition of group, or level-2, variables aim to reduce the level-2 random intercept residual variance (τ_0^2). This leads to an expanded model in which the group-dependent regression coefficients $\beta_{0j}$and β_{1j} from Eq. 2 and Eq.5 now include a level-2 variable *Z* to produce Eq.7 and Eq.8. Substitution back into the basic model (Eq.1) leads to the model in Eq.9.

(Eq.7) $\beta_{0j} = \gamma_{00} + \gamma_{01} z_j + U_{0j}$

(Eq.8) $\beta_{1j} = \gamma_{10} + \gamma_{11} z_j + U_{1j}$

(Eq.9) $Y_{ij} = \gamma_{00} + \gamma_{01} z_j + \gamma_{10} x_{ij} + \gamma_{11} z_j x_{ij} + U_{0j} + U_{1j} x_{ij} + R_{ij}$

The addition of the level-2 variable Z leads to a main effect of *Z* ($\gamma_{01} z_j$) as well as a cross-level interaction effect of *X* and *Z* ($\gamma_{11} z_j x_{ij}$). The cross-level interaction effect is the product between a level-1 and level-2 variable that aims to reduce the level-2 random slope residual variance (τ_1^2). In order to help the interpretation of cross-level interactions, it is strongly advised to grand-mean center the component variables X and Z so that the value of 0 has an interpretable meaning (e.g. the average student and school SES respectively) or that it corresponds to a common reference value (e.g. male students, public schools).

The application of cross-level interactions can be approached either inductively or theoretically. The former implies a post-hoc approach of testing level-2 variables based on the presence of a significant random slope. The latter implies their apriori inclusion based on substantive or theoretical arguments, regardless of whether a random slope was found. The decision for which variables to give random slopes, cross-level and within-level interactions will depend on the subject-matter as well as theoretical and empirical considerations. Having a sufficient sample size is important, but especially at the group-level. Including many random slopes increases the degrees of freedom as well as the difficulty in model interpretation. Parsimony should always be a driving factor in model specification.

3.4 Multilevel Logistic Regression

The purpose of logistic regression is to predict the probability (p_i) that some event occurs for an individual (i) conditional on a number of variables. Due to the natural constraints of the probability distribution falling between 0 and 1, p_i is transformed using a logit function which gives it a distribution of values better suited for regression analysis, namely -∞ and +∞. Similar to multilevel linear regression, multilevel logistic regression considers individuals to be statistically dependent on their area of residence or some hierarchical areal unit for which the individuals are nested within. It is this modeled dependence and the ability to partition its variance at the different levels that is the modus operandi of multilevel regression relevant for both statistical and substantive epidemiologic reasons (i.e. improved estimation and improved contextual understanding of area-level measures on individual outcomes). However, while for the linear case this dependence can be quantified using measures such as the intraclass correlation (ICC) discussed above; the components of variance in logistic models are more complicated due to the nonlinear relation between the covariates and dichotomous response variable. As a result, the ICC has statistical and interpretational drawbacks [68,69].

Two alternative measures of interpretation have therefore been proposed. These include the median odds ratio (MOR) and the interval odds ratio (IOR) [68–70]. The MOR depends directly on the area-level variance and is defined as the median odds ratio between any two areas picked at random with differing risk (i.e. what is the median increase in risk for an individual moving to an area with a higher risk). The aim of the MOR is to translate the area-level variance to the more widely understood odds ratio scale which permits the direct comparison of its magnitude to that of the level-1 and level-2 factors. An MOR equal to one, or for which its 95% confidence intervals (95% CIs) overlap one, would indicate no between-area differences in the individual-level probability of the outcome. An MOR and 95% CIs greater than one would indicate between-area heterogeneity and that the area of residence is important for understanding the variations in the individual probability of the outcome. This would then invite the introduction of area-level variables to test whether they can explain any of the between-area variability [68,69].

The interval odds ratio (IOR) is a fixed-effects measure for the level-2 variables that takes the area-level variance into account when interpreting their association with the outcome. The IOR is an interval for odds ratios between two persons with similar covariate patterns, covering the middle 80% of the odds ratios; however smaller or larger intervals

could be selected (e.g. 70% or 90%). The IOR makes it possible to determine whether a level-2 variable is useful to identify high risk areas, or whether the remaining between-area variability is too large for that variable to make a difference. For example, if the IOR for a level-2 variable does not contain one, then this suggests that its effect is large relative to the area-level variance. Conversely, if the IOR for a level-2 variable does contain one, then that variable does not account for a substantial amount of the area-level variability. The width of the IOR, whether it's narrow or wide, gives an indication of the amount of unexplained between-area variation in the propensity of an individual to have the outcome. Thus, while related, the MOR and IOR provide different information useful in the analysis of contextual-level effects [68,69].

In the multilevel framework, observations within a particular geographical area are assumed to be statistically independent of those from another area (regardless of adjacency) thereby ignoring any spatial associations *between* the geographical macro-unit areas [71,72]. Therefore, the multilevel framework has been combined with spatial regression techniques in order to account for the potential of spatial dependency (i.e. spatial autocorrelation) of the area-level residuals [73]. The following section provides a brief review of the mechanisms and methods of spatial dependence in health data.

4.0 Spatial Dependence: Mechanisms, Methods and Models

Spatial (inter)dependence is ubiquitous. As stated in Tobler's so-called 1st Law of Geography: *everything is related to everything else, but near things are more related than distant things*. While simplistic, this interpretation of spatial interdependence as it relates to the interaction between the physical and social environments and reproductive health is appropriate to form the basis of building empirical models. In practice however, accommodating spatial dependence into statistical models is a complex endeavour, which is why it is often ignored or argued as irrelevant. It was recognized over 120 years ago by Sir Francis Galton that drawing inferences from samples that are not statistically independent can yield misleading conclusions, a statistical phenomenon now known as (spatial/temporal) autocorrelation [74]. Several methods and models have been developed capable of accounting for spatial effects (i.e. spatial dependence and/or spatial heterogeneity) [75,76], in which the following paragraphs will briefly describe as a means to introduce the methodologies and terminology used throughout this dissertation.

4.1 Spatial Dependence & Spatial Heterogeneity

In general, spatial dependence exists when the value of a variable at one location is dependent on its values at other locations. It can arise due to spatial interaction effects (e.g. externalities or spill-over effects [73,77]), or from measurement error (e.g. scale mismatch between how a variable was measured and that at which it occurs [78,79]). Spatial autocorrelation is an indicator of spatial dependence in which a variable is correlated with itself in space. Spatial heterogeneity (or non-stationarity) on the other hand refers to structural changes in a dataset related to location, such as differences in the mean, variance, and/or covariance structure of a variable across space (e.g. the relative difference of SES differ between urban and rural regimes [80]). Ignoring these aspects of the data can lead to inefficient or biased estimates resulting in misleading inference. For example, the presence of positive spatial autocorrelation, where high or low values correlate with high or low neighbouring values, results in a loss of information in the context of greater uncertainty, less precision, and larger standard errors. The presence of spatial heterogeneity can result from heteroscedasticity (non-constant error variance) across space and indicate scale-related measurement errors [78,79]. In practice, it can be difficult to distinguish between spatial dependence and spatial heterogeneity, and tests for one may signal the other and vice versa [81,82].

4.2 Spatial Weight Matrices

In spatial analyses, the concept of space is operationalized through the use of spatial weights matrices. Defined as the formal expression of spatial dependence between observations [75], they contain information regarding the neighborhood or connectivity structure in the data in order to assess the extent of similarity between locations and values (e.g. spatial autocorrelation). The researcher must make an assumption regarding the structure of interdependence between any two observations. This is commonly based on adjacency/contiguity (i.e. sharing a common boundary or a specified number of nearest neighbours) or proximity (i.e. number of neighbours within a given distance); however, more complex formalizations are possible such as using a functional distance based on travel time as opposed to Euclidian (straight-line) distance, adding a distance-decay mechanism or even some non-geographic notion of distance [83]. In short, the selection of the spatial weight matrix should be based on some substantive knowledge about the spatial

process being modeled and sensitivity analyses using different weight matrices can be applied to test the connectivity assumptions.

In general there are two basic categories of weight matrices: contiguity-based (i.e. shared borders) and distance-based. Examples of contiguity-based weight matrices include Rook and Queen criterion which symbolize the selection of neighbours to the movement of the corresponding chess pieces (e.g. north-south/east-west for Rook, and all possible directional vertices for Queen). Distance-based weight matrices can include a fixed distance criterion but could include more nuanced notions of distance such as time-travelled distances, perceptive distances, or policy-defined distance [83]. Finally, k nearest neighbours (KNN) is a type of distance-based weight matrix where "k" refers to a specified number of neighbours for each observational unit. It uses the distance between the central points (or centroids) of the areal unit polygons to determine the nearest neighbouring units. It is useful in situations where the areal units are of varying size to ensure that every location has an equal number of neighbours as well as in situations where some areal units are "islands" (i.e. have no contiguous neighbours). KNN weight matrices are asymmetric, that is, area A is B's nearest neighbour but not necessarily visa-versa; whereas Queen and Rook criteria are symmetric. This can have implications on the types of spatial analyses that can be performed [82].

The spatial weight matrix is made up of one row and column for each observational unit using binary (0, 1) codes to define neighbours as 1 and non-neighbours and the focal location as 0 (Figure 8). Neighbours of neighbours can be defined by higher orders of contiguity. Row-standardization transforms the weight matrix so that the values in each row sums to one. Row-standardized weight matrices are useful when wanting to compare different model coefficients.

$$W = \begin{bmatrix} & A & B & C & D & E \\ A & 0 & 1 & 1 & 0 & 0 \\ B & 1 & 0 & 1 & 0 & 1 \\ C & 1 & 1 & 0 & 1 & 0 \\ D & 0 & 0 & 1 & 0 & 0 \\ E & 0 & 1 & 0 & 0 & 0 \end{bmatrix}$$

Figure 8: *n* by *n* binary spatial weight matrix

Elements w_{ij} representing the association between regions *i* and *j* where $w_{ij} = 1$ if i and j are neighbours, $w_{ij} = 0$ otherwise.

There is no real empirical method that can be applied to select the "correct" spatial weight matrix; however, two considerations should be taken into account. The first is theoretical and relates to the hypothesized underlying spatial process that is being

assessed. The other is more technical, and has to do with the tessellation of areal (polygon) unit used, be it irregular shaped administrative areas (e.g. census areas), a uniform grid (e.g. 5x5 km grid), or some other lattice (e.g. Thiessen polygons).

Some suggest selecting the spatial weight matrix based on the strength of the spatial autocorrelation test (e.g. Moran's *I*). Figure 9 shows 6 Morans' *I* scatterplots showing the degree of clustering of a model's residuals using different k-nearest neighbour (KNN) spatial weight matrices. Using the above criteria of largest Moran's *I* test, using a KNN=6 produces the highest Moran's *I*.

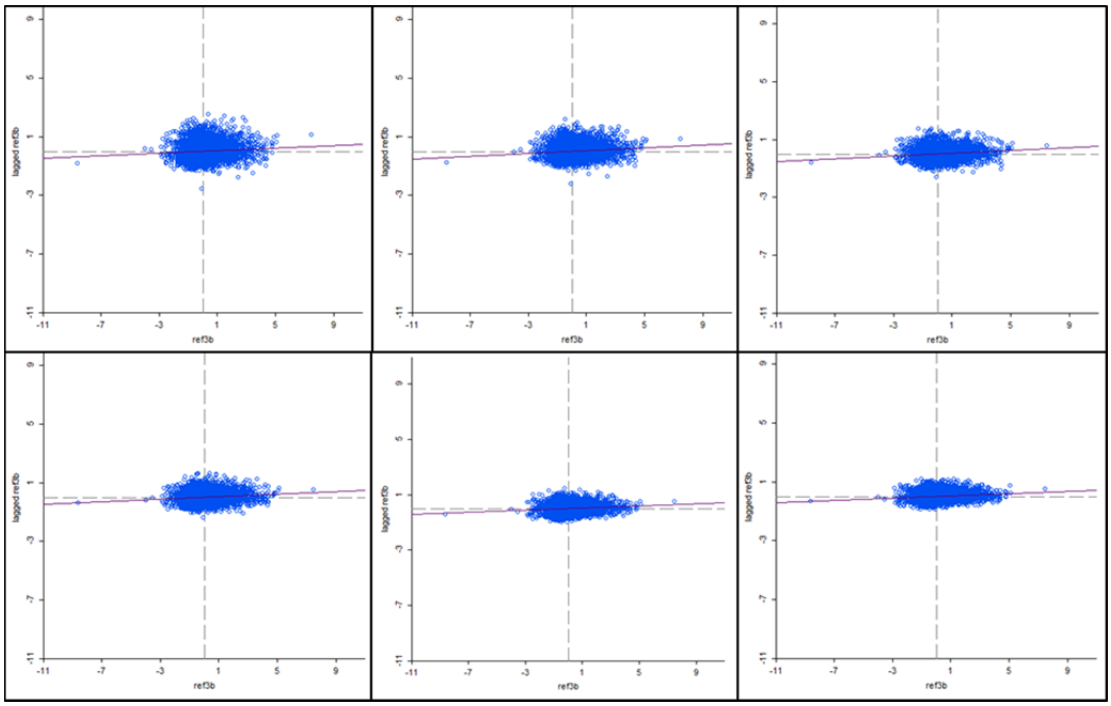

Figure 9: Moran's *I* scatterplots showing the degree of clustering of model residuals using different KNN spatial weight matrices.

Top row, left to right: KNN-4: I = 0.0450; KNN-6: I = 0.0480; KNN-8: I = 0.0472;
Bottom row, left to right: KNN-10: I = 0.0443; KNN-15: I = 0.0399; KNN-20: I = 0.0384.

There are several tests of spatial autocorrelation. In general, they measure the tendency for high or low values to cluster or correlate more closely in space with other high or low values than would be expected if the data were randomly distributed. Global tests for spatial autocorrelation measure this tendency across the entire study area, while local indicators of spatial association (LISA) identify local "hotspot" clusters of high or low values between areal units [84], or determine the distance beyond which no discernable spatial autocorrelation is measured [85]. For example, the Moran's *I* statistic measures the degree of linear association between an attribute (y) at a given location and its weighted average at

neighbouring locations (Wy). It can be graphically displayed using scatterplots (Figure 9) and/or as hotspot cluster maps (Figure 10) [84].

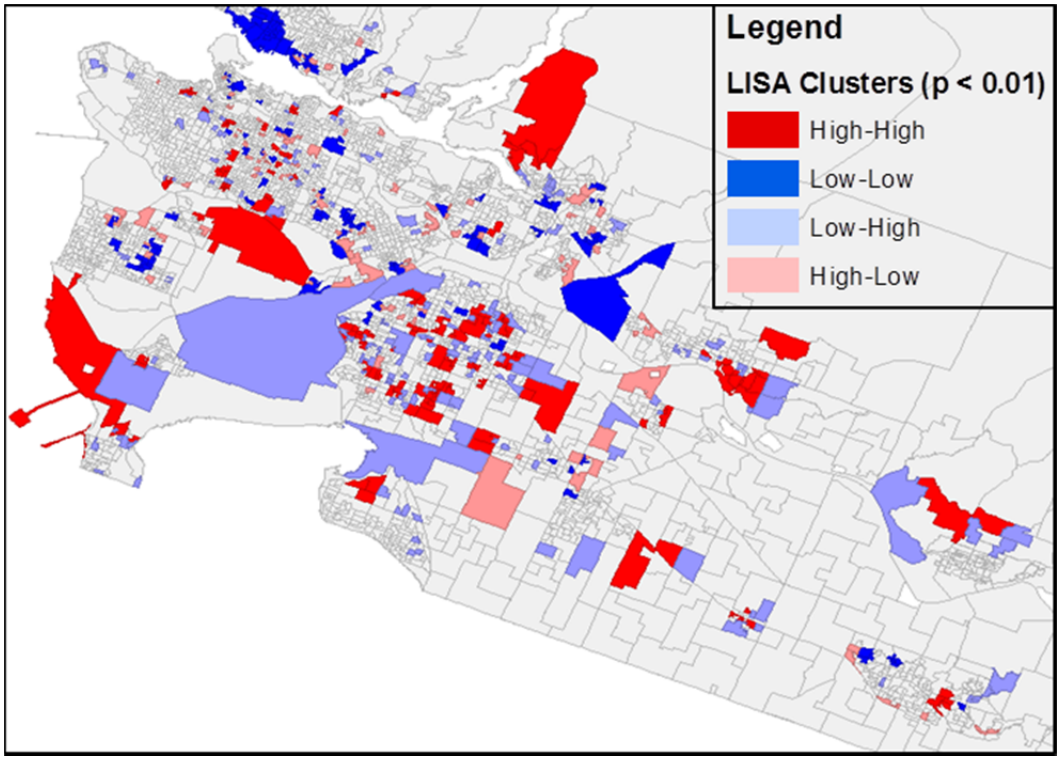

Figure 10: Moran's *I* cluster map shows the clustering of model residuals between the areal units (DAs) using a 6-KNN spatial weight matrix.

4.3 Spatial Regression Models

The spatial lag model is a linear regression model that explicitly incorporates spatial dependence into its framework by adding a "spatially lagged" dependent variable as an independent variable on the right-hand side of the regression equation. Sometimes also called a *spatial autoregressive model,* this model is appropriate when it is believed that the values of the dependent variable in the focal neighbourhood is directly influenced by the value of the dependent variable in neighbouring units above and beyond the presence of other covariates. Alternatively, if it is believed that a latent spatially clustered process or variable is influencing the dependent variable in the focal and neighbouring units, then the spatial error model may be more appropriate [86].

A significant spatial lag term may indicate strong spatial dependence, but may also indicate the presence of MAUP regarding the mismatch of spatial scales between the spatial process under study and its measurement by some proxy variable. A significant spatial

error term indicates spatial autocorrelation in the errors, likely due to the presence of important unmeasured explanatory variables not included in the model [81].

Thus, for example, let the dependent variable be the prevalence of maternal smoking while pregnant in a neighbourhood. It could be that this is partly a function of maternal smoking in adjacent neighbourhoods, rather than just being related to common unmeasured variables in those neighbours. Hence the spatial lag model might offer insight into spatial externalities of the spatial transmission of (un)healthy behaviours, and implies that the spatial dependence is an interesting phenomenon to investigate. The spatial error model on the other hand implies that the pattern of spatial dependence is attributable to unmeasured covariates (i.e. the stochastic components) only. Hence, spatial error models are rarely theory-driven, and employed mainly to accommodate nuisance spatial dependence [83,86].

4.4 Rate Smoothing

Rate smoothing is one way to address the variance instability of raw rates in populations of different sizes. Smoothed rates are stabilized by borrowing strength from neighbouring spatial units in which the amount of smoothing is inversely proportional to the underlying size of the population at risk. That is, areas with small population counts will produce raw risk rates with large standard errors and will therefore undergo greater smoothing adjustments. There are several different flavours of rate smoothers [87].

Excess risk maps (aka standard mortality rates or SMRs) are used to visualize the degree to which areal unit rates exceed or are below the expected average risk. Excess risk maps are based on the ratio between the observed to expected counts of an event (SMR = Observed/Expected). Expected counts are the product of the local risk rate and the average overall risk for the study region. Unlike smoothers, excess risk maps only re-scale the raw rate so that the magnitude, not the order, of the original data changes. These maps however do not provide information on statistical significance of the rates [82,87].

The Spatial Rate smoother is similar to a spatial moving average in which raw rates are computed for each areal unit as well as its neighbours as defined by the chosen weight matrix. It's application is useful to identify spatial regimes in the data, a form of spatial heterogeneity which implies structural differences across space [82,87].

The Empirical Bayes (EB) smoother is based on the raw rate for each areal unit that is averaged using a *prior* estimate based on the entire study region (i.e. the overall (global) population mean and variance). In large study areas where regional characteristics may

influence the rates, a local prior can be substituted over the global one as defined by a given spatial weights matrix (so called the spatial EB smoother). When selecting between smoothers, consideration should be given to the area where strength is borrowed from and its representativeness of the underlying risk in the local area [82,87].

The advantage of smoothing can be a double-edged sword. The benefits include the removal of spurious outliers and the ability to represent overall patterns beyond particularly high and low values. The flipside is that results can be quite sensitive to a given smoother, and over-smoothing may conceal interesting extreme cases. It is wise to perform a series of sensitivity analyses using different smoothers to gauge the degree of change in the results. EB standardization procedure is used in the global Moran's *I* scatterplot and LISA maps. It directly standardizes the raw rates to obtain a constant variance with a zero mean and standard deviation of one.

5.0 Perinatal Data Registries and Adverse Pregnancy Outcomes

5.1 The BC Perinatal Database Registry

The use of existing birth registries to identify environment and SES-related health relationships is a useful tool in public health monitoring and surveillance research which has been in practice for decades in Scandinavian countries [27,88–91]. In Canada, the Canadian Perinatal Surveillance System (CPSS) is a partnership between several federal agencies together with the provinces and territories which are responsible for collecting specific indicator variables and sharing them with the CPSS for national assessment and interpretation [92,93]. While national surveillance is important, the resolution of the data collected by the CPSS is too low for research into putative environmental exposures and accessing provincial registry data is often better suited for this task.

The British Columbia Perinatal Database Registry (BCPDR) managed by Perinatal Services BC (PSBC) is a comprehensive, province-wide perinatal database collected for the purpose of evaluating perinatal outcomes, care processes and resources, ultimately improving maternal, fetal, and newborn care. The Registry accounts for 99% of births in BC collected from facilities throughout the province on a voluntary basis. Data collected includes: antenatal, intrapartum and postpartum maternal and infant care and outcomes, as well as neonatal follow-up and outcomes including linking to BC Vital Stats to provide infant death data. Data quality is addressed by validation edits, errors and warnings as part of the data entry software program, period end checks and reports [94]. Third party data access is provided by a Partnership Accord/Memorandum of Agreement between all BC Health

Authorities and PSBC through the *Freedom of Information and Privacy Protection Act*. Data release applications are reviewed by the Research Review Committee with representation from health care providers, health authorities, and academic organizations [95]. One shortcoming of the BCPDR, as well as many birth registries in Canada, is the handling of congenital anomaly surveillance. The complete and reliable ascertainment of congenital anomalies can be the most challenging aspect of maintaining a high quality surveillance system. Therefore despite having the data, congenital anomalies are not assessed in this dissertation.

5.2 Adverse Pregnancy Outcomes

5.2.1 Measures of Birth Weight

When considering measures of birth weight in studies of APOs, it is important to differentiate between three related terms sometimes used interchangeably but which are not necessarily synonymous. Low birth weight (LBW) refers to infants born weighing less than 2,500 grams regardless of gestational age, although distinctions between preterm, term and post-term LBW can be made [96]. LBW is the result of two overlapping but distinct etiologies, PTB and/or IUGR, the determinants and health consequences of which are quite different [17]. Therefore, the use of LBW in epidemiological studies can be problematic due the ambiguity of its underlying etiology. Small-for-gestational age (SGA) refers to infants whose weight falls below a threshold cut-point of a given percentile (e.g. the 10^{th} or 3^{rd}) using sex-specific birth weight for gestational age distribution curves [97], although further customization based on maternal characteristics have been argued [43–45]. Intrauterine growth restriction (IUGR, or fetal growth restriction FGR) is defined as the process that leads to SGA or LBW by some aetiology that limits the growth of the fetus from its full potential [98,99]. It is diagnosed during the antenatal period from measurements of fetal growth using ultrasound techniques and plotting against standardized fetal growth curves for the given gestational age [100]. If measurements and weight fall below the tenth percentile, fetal growth restriction is suspected and therapeutic management can be initiated. The determination of whether the FGR is asymmetrical or symmetrical gives clues to the causal mechanism. Symmetric FGR describes a fetus that is proportionally small and may just be its constitutional make-up; conversely, asymmetrical FGR indicates that a fetus is undernourished and is directing its energy away from the liver, muscle and fat to

prioritize growth of vital organs such as the brain and heart. Asymmetric FGR is indicative of placental insufficiency and is associated with worse perinatal outcomes [99].

5.2.2 Preterm Birth

Preterm birth (PTB, deliveries prior to 37 completed weeks of gestation) is considered as one of the most important perinatal challenges facing industrialized countries due to high infant mortality, serious long-term morbidities and elevated health care costs [101]. Clinically, PTB is categorized as either 1) spontaneous preterm labour with either intact membranes or preterm premature rupture of membranes (PPROM); or 2) medically indicated (iatrogenic) for maternal or fetal conditions such as preeclampsia, haemorrhage, non-reassuring heart rate and IUGR in which labour is either induced or the fetus is delivered by pre-labour Caesarean section [102].

Incidence rates in many industrialized countries are rising, largely due to increases in medically indicated determinants such as labour induction and prelabour caesarean delivery but also attributed to a rise in twin/multiple births and better estimates of gestational age via ultrasound [102,103]. When divided into early (< 31 weeks), moderate (32-33 weeks) and mild (34-36) PTB, the largest relative and absolute increases are in the latter category which also account for the largest proportion of PTBs in Canada and the United States. Therefore, while the relative risk (RR) of infant death among mild PTB is smaller compared to earlier PTB categories, etiologic fraction of mild PTB in infant death has a larger population-level impact due to its much higher incidence [104].

The rates of spontaneous preterm parturition, either with intact or ruptured membranes (PPROM),have been stable over the past decade but accounts for over half of PTB cases [102]. The proposed mechanisms that initiate this syndrome include factors that stimulate the inflammation pathway such as infection, stress, vasculopathic ischemia and other immunological and endocrine disorders [105–107]. Meanwhile, the observed increase in iatrogenic PTBs reflects the increase in mild PTB and prelabour caesarean delivery. An analysis in Canada showed that the largest indication and overall increase in prelabour caesarean delivery was due to pregnancy induced hypertension/preeclampsia (PIH/PE) and poor fetal growth[108]. Therefore regardless of whether it's spontaneous or iatrogenic PTB, both are associated with and display pathoetiologic mechanisms related to air pollution exposure [109–111].

5.2.3 Pregnancy Induced Hypertension & Preeclampsia

Preeclampsia (PE) is a multisystem pregnancy disorder unique to humans that affects between 2 to 7 percent of pregnancies and is characterized by systemic endothelial dysfunction and increased vascular resistance, platelet aggregation and coagulation [112,113]. Clinical features include new-onset (i.e. pregnancy induced) hypertension (PIH) and proteinuria after 20 weeks gestation; however, its pathogenesis is thought to start shortly after implantation with impaired of normal placentation leading to insufficient placental perfusion that eventually, depending on severity, cascades into the maternal PE syndrome [114]. Immune maladaptation, inflammatory response and oxidative stress are considered key mechanisms, which is evidenced by many of the maternal risk factors. This is includes being nulliparous or having limited exposure with a partner prior to conception (primipaternity), both of which gives clues to an immunological pathogenesis and may explain the higher risk in young women under 20 years old [112,113]. On the other hand, PIH/PE share many risk factors and pathophysiological abnormalities to those of cardiovascular disease (CVD). This includes chronic hypertension, diabetes mellitus, obesity and advanced maternal age, all of which are associated with excess oxidative stress [114–116]. Interestingly, smoking is protective against the development of PIH/PE ; however this protection may be limited to smoking in the third trimester [117]. Smoking may exert its protective effect by increasing VEGFA expression in the early stages of pregnancy [118], and/or by reducing levels of VEGF antagonists such as soluble Flt-1 (sFlt-1) and soluble endoglin (sEng) released by placental villi in compromised placentas [117]. This proposed mechanism may also tie in with HO-1 status and the increased presence of CO from smoking as a scavenger of sFlt and sEng [119,120]. To date, delivery of the placenta is the only known treatment; therefore PIH/PE is a major risk factor for PTB and IUGR and until recently has been largely neglected as a potential mediating outcome on the causal pathway between air pollution and APOs [110].

5.2.4 Gestational Diabetes

Gestational diabetes mellitus (GDM) is a conditions that affect between 3-6% of pregnancies, with rates increasing in Canada [121,122]. GDM is associated with increased risk of maternal and fetal/infant morbidities and mortality [121]. Women who develop GDM have an increased lifetime risk of developing type 2 diabetes later in life [123,124]. Risk factors include increased body mass index (BMI), family history, and older maternal age [124]. Recently, there is accumulating evidence supporting their association with

exposure to air pollution [125–127]; therefore, GDM should now be considered a mediating outcome on the causal pathway between air pollution and other APOs co-related with air pollution.

6.0 Exposure Assessment

6.1 Exposure Assessment Terminology

The meaning of the terms 'environment', 'risk' and 'exposure' can differ among different disciplines; this is particularly true for interdisciplinary fields such as epidemiology. The use of standardized and consistent language is critical to effective communication; therefore some key terms require to be explicitly defined at this time. The term *agent* will be defined as any chemical (e.g. particulate matter), biological (e.g. black mold), physical (e.g. noise, heat) or psychosocial stressor (e.g. poverty, violence, housing quality) to which an individual or population is exposed [128,129]. *Exposure* is then the contact of an agent at the interface between humans and their environment for some period of time [130]. Quantitatively, this could be a chemical concentration in a carrier medium (e.g. air, water, soil, food), decibels, years of education; however, the exposure could also be assessed qualitatively or semi-quantitatively such as present/absence, Likert or relative scale (e.g. high, medium, or low).

In order for exposure and dose values to be of much benefit, they need to be related into interpretable descriptors of risk. *Risk* is defined as the probability of an adverse effect occurring. There are a variety of ways to model the linear or non-linear relationship of exposure to individual or population risk [131]. In risk assessment, a risk manager may be interested in terms of a hypothesized 'maximally exposed individual' to serve as the upper limit of a risk probability or in terms of hypothesized scenarios (e.g. lifetime risk of cancer for a homeowner 2 km from an oil refinery). In observational epidemiology however, obtaining population risk is often the goal (e.g. what is the probability of additional cases of disease per unit increase in exposure) conditional on age, ethnicity, lifestyle, SES, etc.

6.2 Exposure Assessment Quantification

The quantification of exposure can be approached from three distinct and independent methods which will invariably dictate the type of exposure model to be employed. They include: point-of-contact, reconstruction via the use of biomarkers, and scenario evaluation. Each reflect different approaches to data measurement and application (i.e. direct or indirect measure of exposure or dose) with its own strengths and weaknesses.

The approach taken ultimately depends on the purpose of the exposure assessment s well as the availability of resources and quality data.

With respect to observational or environmental epidemiologic studies, often the main purpose of the exposure assessment is to establish an exposure-incidence or dose-effect relationship. This usually involves estimating historical exposures for a segment of the population based on geography or the population at risk for which scenario development has successfully been used [132]. Scenario evaluation is an indirect estimate of exposure. This method typically uses measured concentration data in a bulk media or location in combination with a modelling procedure to either extrapolate or interpolate exposure concentrations to other media or locations for which measurements do not exist [131]. Environmental fate [133,134], land-use regression (LUR) [135,136], and dispersion models [137] are common examples of scenario evaluation models. Focus here will be on the application of LUR models with respect to environmental epidemiological research.

An exposure model is a conceptual or mathematical representation of the exposure process by combining real measurements and applying various assumptions to provide estimates of exposure/dose for a defined population [128]. LUR models are a type of empirical model that estimates the statistical relationship (e.g. regression) between pollutant measurements and land-use characteristics as independent variables to predict concentrations and apply them to unknown locations using geographic information systems (GIS). LUR models have successfully been used to predict within-city air pollutant concentrations using predictor variables such as traffic density, road length, proximity to major road or other sources (e.g. gas stations, airports) [136,138–140]. A national LUR model was developed by Hystad et al. (2011) that captured both between and within-city pollution variability across Canada. $PM_{2.5}$, NO_2 and VOC air pollutants were applied to street block-face points to determine population exposure estimates. [141].

While the application of LURs in environmental air pollution epidemiologic studies has many advantages over other methods [132,135], they do have certain limitations. Although not limited to LUR models, the presence of measurement error and exposure misclassification is of upmost importance. Distinction between two components of measurement error should be made. Berkson-like error can be considered as part of the true exposure not predicted from the model and will inflate the standard errors of the health effect but induces very little to no bias in the magnitude of the effect estimate. Classical-like error on the other hand results from uncertainty in the measurement of the

exposure model parameters and can both inflate the standard errors as well as bias the effect estimate [142,143].

The magnitude of the error in health effect estimates depends partly on the study design as well as the pollutant being modeled. Nethery et al (2008) conducted a series of studies in the Vancouver BC region that evaluated the ability of LUR models to predict personal exposure to air pollutants in a cohort of pregnant women. She concluded that the use of outdoor concentration estimates were good proxies for exposure [144], and that specifically for $PM_{2.5}$, incorporating mobility patterns into the models did not markedly improve the exposure assessments based on personal monitoring [145]. This was attributable to the fact that $PM_{2.5}$ has a relatively homogenous distribution within communities compared to an air pollutant such as NO_2 which has much greater local spatial variability [145,146]. This was also observed for the LUR model by Hystad et al. [141].

Understanding the impact of environmental stressors on human health is a complex undertaking. In light of these challenges, explicit attention to a relevant theoretical framework is critical to understanding, assessing, and communicating cumulative risk burdens. The challenge then becomes how to develop the necessary models and evaluation methods to clarify the etiologic pathways and mechanisms that lead to adverse health outcomes that often disproportionately affect a specific sub-population.

7.0 References

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Chapter 3: Heavy smoking during pregnancy as a marker for other risk factors of adverse birth outcomes: a population-based study in British Columbia, Canada

Erickson AC, Arbour LT. Heavy smoking during pregnancy as a marker for other risk factors of adverse birth outcomes: a population-based study in British Columbia, Canada. *BMC Public Health*. 2012;12(1):102.

Abstract

Background: Smoking during pregnancy is associated with known adverse perinatal and obstetrical outcomes as well as with socio-economic, demographic and other behavioural risk factors that independently influence outcomes. Using a large population-based perinatal registry, we assess the quantity of cigarettes smoked for the magnitude of adverse birth outcomes and also the association of other socio-economic and behavioural risk factors documented within the registry that influence pregnancy outcomes. Our goal was to determine whether number of cigarettes smoked could identify those in greatest need for comprehensive intervention programs to improve outcomes.

Methods: Our population-based retrospective study of singleton births from 2001 to 2006 (N=237,470) utilized data obtained from the BC Perinatal Database Registry. Smoking data, self-reported at the earliest prenatal visit, was categorized as: never, former, light (1 to 4), moderate (5 to 9), or heavy smoker (10 or more per day). Crude and adjusted odds ratios (AOR) with 95 percent confidence intervals (95% CI) were calculated using logistic regression models for smoking frequency and adverse birth outcomes. A partial proportional odds (pp-odds) model was used to determine the association between smoking status and other risk factors.

Results: There were 233,891 singleton births with available smoking status data. A significant dose-dependent increase in risk was observed for the adverse birth outcomes small-for-gestational age, term low birth weight and intra-uterine growth restriction. Results from the pp-odds model indicate heavy smokers were more likely to have not graduated high school: AOR (95% CI) = 3.80 (3.41 - 4.25); be a single parent: 2.27 (2.14 - 2.42); have indication of drug or alcohol use: 7.65 (6.99 – 8.39) and 2.20 (1.88 – 2.59) respectively, attend fewer than 4 prenatal care visits: 1.39 (1.23 – 1.58), and be multiparous: 1.59 (1.51 – 1.68) compared to light, moderate and non-smokers combined.

Conclusion: Our data suggests that self-reports of heavy smoking early in pregnancy could be used as a marker for lifestyle risk factors that in combination with smoking influence birth outcomes. This information may be used for planning targeted intervention programs for not only smoking cessation, but potentially other support services such as nutrition and healthy pregnancy education.

1.0 Background

Smoking during pregnancy is associated with known adverse perinatal and obstetrical outcomes [1-4]; however, it remains unclear the magnitude as to which adverse outcomes are related to cigarette smoke itself versus surrounding factors difficult to quantify and control. For instance, socio-economic status (SES) and psychosocial stress are both associated with adverse birth outcomes [5-7] as well as with prevalence of smoking during pregnancy [8-10]. These observations are supported by the mounting biological evidence for a stress-related psychoneuroendocrine process contributing to the underlying etiology of adverse fetal development [11]. The linkages between socially patterned adverse health behaviours and outcomes are difficult to understand let alone separate and measure. Therefore, it may be beneficial to use (heavy) smoking during pregnancy as a marker for latent and unquantifiable risk factors that also affect outcomes.

In a recent report assessing the number of cigarettes smoked during pregnancy and adverse birth outcomes in the Qikiqtaaluk (Baffin) region of Nunavut, 'heavy smokers' (greater than ten cigarettes per day) had significantly worse birth outcomes than non- and light smokers [12]. In the Qikiqtaaluk population where 80 percent of pregnant mothers smoke, it was surprising to observe what resembles a threshold effect of heavy smoking on adverse birth outcomes, particularly birth weight. A dose-response relationship was also observed between level of smoking during pregnancy and higher self-reporting of alcohol or drug use (predominately marijuana). Despite certain limitations, the results led to the conclusion that heavy smoking may be a marker for additional risk factors and be used to identify high risk populations for targeted intervention [12].

In addition to the inter-relationship between adverse birth outcomes, SES and psychosocial stress mentioned above, heavy smoking could also be marker for poor nutritional status [13]. Smokers in general are shown to have poorer nutritional profiles than non-smokers in which behavioural and biological factors independently account for the differences, particularly micronutrients, essential minerals and vitamins [14, 15]. While smokers tended to have reduced dietary intake of some micronutrients, the observed lower

blood/serum concentrations were primarily attributed to the increased turnover of micronutrients via an inflammatory response caused by the oxidative stress of smoking. Further, in certain cases the inflammation ascribed effect was more pronounced in long-term and heavy smokers [14]. The effects are further confounded amongst pregnant women where it has been shown that heavy smoking, low social class, renting accommodation, and low education predict poor dietary intake [16].

As important as understanding the etiology of adverse birth outcomes, is identifying those at particular risk who might benefit from intervention with the goal of improving outcomes at the population level. The purpose of this study is two-fold: 1) to assess the quantity of cigarettes smoked and the magnitude of adverse birth outcomes, and 2) determine the association of quantity of cigarettes smoked with other socio-economic and behavioural risk factors documented within the registry that also influence pregnancy outcomes. We used a well-established perinatal registry database to ask the question: can high quantities of cigarette use reported at the first prenatal visit be used as a surrogate to identify high risk mothers for targeted support services throughout pregnancy?

2.0 Data and Methods

This population-based retrospective study of all singleton births (live born and stillbirths) in British Columbia from 2001 to 2006 (N=237,470) utilized the Perinatal Services British Columbia (PSBC) Perinatal Database Registry, and included information on maternal-infant health status and outcomes, reproductive history, socio-demographics and residential postal codes. The BCPDR accounts for 99% of about 45,000 births and stillbirths per year occurring in the province from 20 weeks gestation or weighing at least 500 grams at birth. Third party data access is provided by a Partnership Accord /Memorandum of Agreement between all B.C. Health Authorities and the PSBC through the *Freedom of Information and Privacy Protection Act* [17]. Research ethics board approval was granted by the University of Victoria (ethics protocol #: 11-043).

The outcome variables included low birth weight at term (LBW <2,500g with ≥ 37 weeks gestation), preterm birth (PTB - between 20 and 36 completed weeks gestation), intra-uterine growth restriction (IUGR –identified during the antenatal period using ultrasound imaging growth parameters), postnatal small-for-gestational age below the third and tenth percentiles for weight and sex using BC specific birth charts (SGA-3 and SGA-10 respectively) [18], and stillbirths (≥ 20 weeks gestation or ≥ 500g). Out-of-province (n=926), records missing geographic data on maternal area of residence (n=129), and

records not meeting the criteria of a recorded birth in BC (< 20 weeks gestation and < 500 grams birth weight, n=12) were excluded. Outcomes were reviewed for completeness and checked for double counting between variables (e.g. stillbirth and SGA).

Smoking data is usually collected at the first prenatal visit from 12-18 weeks gestation and is categorized in the Registry as "never", "former", and "current". The number of cigarettes smoked per day by current smokers was available as an additional continuous variable and was categorized into three levels of daily maternal cigarette use: light (1 to 4), moderate (5 to 9), and heavy (10 or more). In terms of former smokers, it is unknown when in relation to the pregnancy cessation took place prior to the first prenatal visit. Despite being non-smokers, former smokers were not combined with the 'never' smoked group due to significant maternal characteristic differences between them. The additional individual-level variables include: maternal age, reproductive history (parity ≥ 1), number of antenatal care visits, co-morbidities such as diabetes, gestational diabetes and hypertension during pregnancy, pre-pregnancy weight, indication of drug or alcohol use, number of school years completed and single parent status (indication of support during and after the pregnancy).

Bivariate odds ratio (OR) tests and 95 percent confidence intervals (95% CI) were calculated to assess the influence of each covariate on birth outcomes with the results informing which covariates to include in the models. Crude and adjusted ORs with 95% CIs were calculated using logistic regression to assess the influence of smoking rates on outcomes. Sensitivity analyses were conducted to assess the influence of attrition due to missing data for some covariates. This included bivariate OR tests to determine the likelihood of adverse birth outcomes and maternal characteristics between records with and without data.

In order to determine the association between the covariate risk factors and the different levels of maternal smoking, a specialized case of an ordered logistic model was used called the *partial proportional odds (pp-odds) model*. An ordered (ordinal rank) logistic model is equivalent to a series of binary logistic regressions where the different levels or group ranks of the dependent variable are combined and contrasted [19]. In this case, there are four ordinal levels of smoking status (Never, Light, Medium and Heavy) where: Level 1 is contrasted with Levels 2,3, and 4 combined; Levels 1 and 2 combined versus Levels 3 and 4 combined; and Levels 1,2, and 3 combined versus Level 4. The pp-odds model is less restrictive compared to a regular ordered logistic model (also known as a parallel-lines or proportional-odds model), which assumes all β regression coefficients to be parallel. The

pp-odds model eases this restriction allowing some β coefficients to be the same and some to differ [19]. Former smokers were not used in the pp-odds analysis due to its non-ordinal status. Interactions between covariates were checked with no significant interaction effects observed. All analyses were conducted in *Stata 11 IC* [20].

3.0 Results

Between 2001 and 2006, there were 236,403 singleton births ≥ 500 grams or over 20 weeks gestation in BC. Among them, 26,564 (11.2%) were active smokers, 197,583 (83.6%) reported never smoking, and 12,256 (5.2%) were former smokers. Of the active smokers, 7,806 (3.3% of total *N*) were light smokers (1-4 cigarettes/day), 5,839 (2.5%) were moderate smokers (5-9 cigarettes/day), 10,407 (4.4%) were heavy smokers (≥ 10 cigarettes/day), and 2,512 (1.1%) had missing data on the number of cigarettes smoked per day which were excluded from the analysis. The distribution of daily cigarette consumption was exponential with notable spikes at increments of five cigarettes per day (Figure 11). A comparison of the maternal characteristics across smoking groups is provided in Table 2.

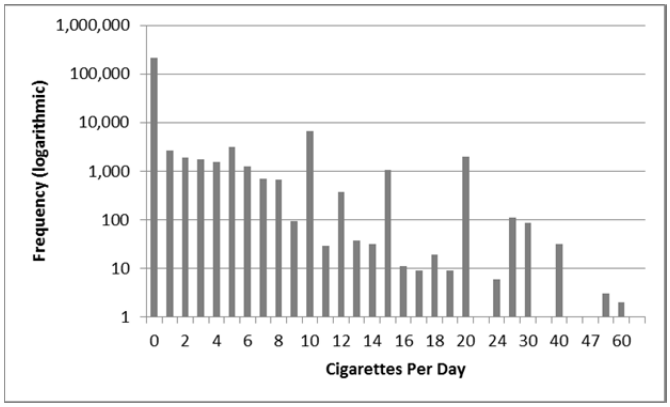

Figure 11: Distribution of Maternal Daily Cigarette Consumption in BC, 2001-06

Maternal characteristics varied substantially across levels of maternal smoking (Table 2). Mothers who were heavy smokers were more likely to be multiparous, a single parent, had not completed high school, be identified for alcohol or drug use and attended fewer prenatal care visits. Heavy smokers were less likely to have had hypertension during the pregnancy and all smokers were less likely to have gestational diabetes. The highest proportion of smokers was under 25 years of age, but tended to be light smokers (inter-quartile range, IQR = 3-6-10). In contrast, the smaller proportion of older mothers (≥ 35) who did smoke tended to be heavy smokers (IQR = 4-10-10). Within age cohorts, a third of all mothers less than 20 years of age and nearly a quarter of women aged 20 to 24 reported smoking with 11.5 and 9 percent of those being heavy smokers respectively. Conversely, ten

percent of the oldest three age cohorts report smoking but had roughly twice the proportion of heavy smokers as light smokers (3.6 and 1.6 percent respectively). Consistent with the youngest group reporting the greatest proportion of current smokers, the two youngest age cohorts also had the highest proportion of former smokers, 13.1 and 8.5 percent respectively.

Further bivariate OR tests with maternal age revealed that women under the age of 30, but particularly teens (under 20) and those 20 to 24 were significantly more likely to be identified for drug use, OR(95% CI) = 9.06(8.19-10.03) and 4.36 (4.00-4.74) respectively; alcohol use, OR(95% CI) = 9.44 (8.13-10.97) and 3.87(3.40-4.42) respectively; and attend fewer than 4 prenatal care visits, OR(95% CI) = 4.45(3.91-5.07) and 2.35(2.12-2.60) respectively compared to women 30 to 34 years of age. Lack of high school graduation for women aged 20 to 24 were also low compared to the 30-34 age cohort, OR(95% CI) = 9.80(8.60-11.39). Furthermore, among women under 25 years of age, those who were heavy smokers were over ten times more likely be identified for drug use than non-smokers whereas light and moderate smokers had about half the risk, OR(95% CI) = 10.59 (9.46-11.86) and 6.67 (5.79-7.67) for heavy and moderate smokers respectively. While heavy smokers under 25 years old also had the highest risk for alcohol indication, low prenatal care attendance, single parent and no grade 12 educations, the differences between levels of smoking were less stark.

Table 2: Maternal Characteristics by Smoking Status in BC, 2001-2006

Characteristic		Births by Smoking Status,* % Never *n = 197,583*	Former *n = 12,256*	1 – 4 *n = 7,806*	5 – 9 *n = 5,839*	10 + *n = 10,407*	Missing *n = 2,512*	Total (% missing)
Age, yr	< 20	2.3	7.8	14.0	12.2	9.2	11.8	8,620 *(3.5)*
	20-24	12.4	24.3	32.4	32.7	30.3	29.0	35,817 *(2.0)*
	25-29	27.9	29.5	26.8	27.2	26.8	25.7	65,877 *(1.0)*
	30-34	34.7	24.5	17.4	17.3	20.3	21.1	76,616 *(0.7)*
	35-39	18.7	11.5	7.7	8.8	10.8	10.1	40,808 *(0.6)*
	40+	4.0	2.4	1.7	1.8	2.5	2.2	8,665 *(0.7)*
Parity ≥1	No	44.3	59.3	54.7	47.3	40.2	52.5	107,381 *(1.2)*
	Yes	55.7	40.7	45.3	52.7	59.8	47.5	129,022 *(0.9)*
Single Parent	No	92.7	87.1	76.5	77.8	75.1	75.6	214,054 *(0.9)*
	Yes	3.7	8.7	15.0	15.1	16.7	18.3	12,726 *(3.6)*
	Unknown	3.6	4.1	8.6	7.1	8.2	6.1	9,623 *(1.6)*
Has Grade 12†	No	0.8	3.0	5.2	5.2	5.4	3.1	3,301 *(0.7)*
	Yes	10.7	12.9	9.6	9.4	6.5	6.7	24,908 *(2.4)*
	missing	88.5	84.1	85.2	85.4	88.1	90.2	208,194 *(1.1)*
Gestational	No	93.3	94.6	96.2	95.8	95.1	94.7	221,256 *(1.1)*
diabetes	Yes	6.7	5.4	3.8	4.2	4.9	5.3	15,147 *(0.9)*
Pre-existing	No	99.6	99.7	99.6	99.6	99.4	99.6	235,465 *(1.1)*
diabetes	Yes	0.4	0.3	0.4	0.4	0.6	0.4	938 *(1.2)*
Hypertension	No	97.8	97.1	98.1	98.0	98.2	97.8	228,674 *(1.1)*
in pregnancy	Yes	2.2	3.0	1.9	2.0	1.8	2.2	5,272 *(1.0)*
Alcohol Flag	No	99.7	98.1	95.9	96.6	95.1	93.8	234,290 *(1.0)*
	Yes	0.4	1.9	4.1	3.4	4.9	6.3	2,113 *(7.4)*
Drug Flag	No	99.2	96.9	90.8	90.3	84.6	86.7	231,267 *(0.9)*
	Yes	0.8	3.1	9.2	9.7	15.4	13.1	5,136 *(6.4)*
Pre-pregnancy	<55	21.0	16.4	19.0	19.9	18.8	16.4	48,430 *(0.9)*
weight	55-74	42.9	43.6	38.8	38.6	36.2	35.0	99,973 *(0.9)*
	> 74	14.7	22.0	18.1	18.4	20.3	16.7	36,720 *(1.1)*
	missing	21.5	18.1	24.1	23.1	24.7	31.8	51,280 *(1.6)*
Prenatal Visits	≥ 3	92.1	93.4	92.3	91.2	89.5	85.9	217,461 *(1.0)*
	< 3	1.2	1.2	2.5	3.0	3.4	3.8	3,364 *(2.9)*
	missing	6.7	5.5	5.2	5.8	7.1	10.3	15,578 *(1.7)*

* Likelihood-Ratio Chi-squared tests for independence across the 5 smoking categories were all significant at $p < 0.05$, except pre-existing diabetes (*p=0.06*).
† Maternal education was measured in years of education with '12 years' indicating high school education.

Missing values were a concern in two key covariates, education level and pre-pregnancy weight, therefore sensitivity analyses were carried out to determine the difference in characteristics of those with missing data. Sensitivity analyses on those missing education data (88.1%) revealed small but significantly increased risks for most adverse birth outcomes (OR range between 1.11 – 1.29) and no statistical difference for stillbirths. Light, moderate and former smokers were less likely to be missing education data compared to those who never smoked, while there was no difference between heavy smokers and never smokers with missing education data. However, overall differences in age and cigarettes consumption were negligible with the IQR of those with and without data being 3-6-10 and 3-7-10 respectively for cigarettes use among smokers and an identical IQR for age. The sensitivity analyses on those records missing pre-pregnancy weight data (21.7%) demonstrated significantly increased risks of PTB and stillbirths, a significantly lower risk of IUGR, and no statistical difference for the other outcomes. All levels of smoking were significantly more likely to be missing pre-pregnancy weight data compared to mothers who never smoked, although the IQR of cigarette use between those with and without data were similar (3-6-10 and 3-7-10 respectively). In terms of other maternal characteristics, there were some differences in the variables which were more or less likely to be missing data, however no clear trends were observed.

Figure 12 shows the adjusted odds ratios of adverse birth outcomes with maternal smoking status (differences between crude and adjusted ORs were unremarkable). Compared to mothers who never smoked, there was a significant dose-dependent increase in risk for all adverse birth outcomes with maternal smoking with the exception of stillbirths. Furthermore, heavy smokers had a significantly greater risk of SGA-3, SGA-10 and IUGR compared to light and moderate smokers. The addition of the education variable attenuated the effect of light smokers for all outcomes resulting in no significant difference compared to non-smokers. Similarly, all observed effects of smoking and PTB were reduced to the null after including the education variable to the model. However, the education variable did not alter the effect of outcomes on heavy smokers while it strengthened the effect of moderate smokers for SGA-3, SGA-10 and LBW.

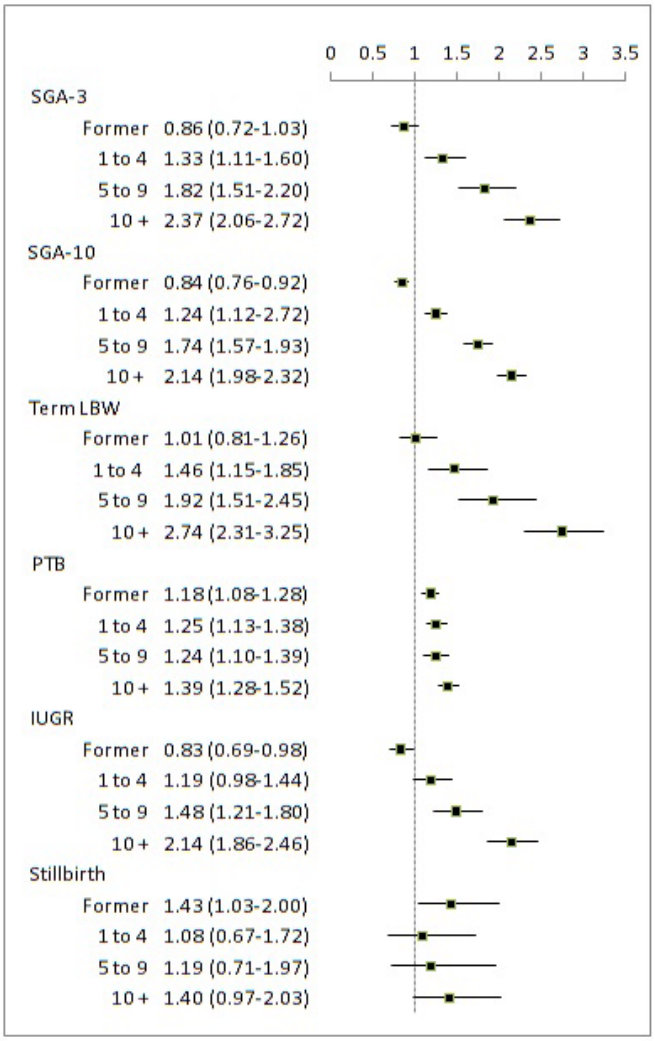

Figure 12: Adjusted Odd Ratios of Adverse Birth Outcomes and Levels of Maternal Smoking
SGA-3 – Small for Gestational Age below the 3rd percentile (*n* = 172,667), SGA-10 – Small for Gestational Age below the 10th percentile (*n* = 172,667), LBW – Low Birth Weight at term (*n* = 161,041), PTB – Preterm Birth (*n* = 172,690), IUGR – Intra-Uterine Growth Restriction (*n* = 172,849), Stillbirth (*n* = 173,397). Tests were adjusted for: maternal age, parity>1, alcohol flag, drug flag, prenatal care visits, prior and gestational diabetes, hypertension during pregnancy, pre-pregnancy weight, and lone parent.

Results from the pp-odds model describe how different covariate risk factors predict higher or lower levels of maternal smoking (Table 3). All variables except older maternal age were risk factors for smoking during pregnancy, but of those, only multiparity and pre-pregnancy weight greater than 74 kilograms predicted heavy smoking over the lower levels of smoking. This is demonstrated by the increasing effect of these two variables across the three comparisons. Older maternal age also predicted higher levels of smoking despite being associated with never smoking. Young maternal age (< 25 years), single parent, drug and alcohol indicators were all strongly associated with maternal smoking across all comparisons, but exhibited their strongest effects for Level-1 (never smoked versus all smokers). For example, women who smoked were 10 times more likely to be indicated for drug use compared to women who never smoked, while heavy smokers were 7.6 times more likely to be indicated for drug use compared to moderate, light and non-

smokers combined. Having three or fewer prenatal care visits and a diagnosis of pre-existing diabetes (*p = 0.06*) met the parallel-lines assumption, and therefore had a constant effect across all levels of comparison. These general trends were sustained with the addition of the education variable into the pp-odds model demonstrating a strong constant effect across all levels of comparison, OR = 3.80 (95% CI 3.41 – 4.25) with a reduced population size of 21,775. Only the variables prenatal care and pre-existing diabetes had their effects significantly reduced to the null (*p = 0.9* and *0.4* respectively).

Table 3: Odds Ratios of Covariate Risk Factors Predicting Level of Maternal Smoking in B.C. 2001 – 2006 (n = 163,867)

Characteristic	OR (95% CI) Level 1 Vs. Level 2+3+4	OR (95% CI) Level 1+2 Vs. Level 3+4	OR (95% CI) Level 1+2+3 Vs. Level 4
Young Maternal Age (< 25)	3.66 (3.52 – 3.80)	3.27 (3.13 – 3.42)	2.86 (2.70 – 3.02)
Older Maternal Age (≥ 35)	0.67 (0.64 - 0.71)	0.71 (0.67 - 0.76)	0.77 (0.71 - 0.83)
Single Parent	2.42 (2.31 - 2.53)	2.25 (2.14 - 2.37)	2.27 (2.14 - 2.42)
Parity ≥1	1.26 (1.22 - 1.31)	1.49 (1.43 - 1.55)	1.59 (1.51 - 1.68)
Alcohol Indication	3.06 (2.63 - 3.57)	2.41 (2.08 - 2.81)	2.20 (1.88 - 2.59)
Drug Indication	10.19 (9.32 - 11.15)	8.17 (7.50 – 8.90)	7.65 (6.99 – 8.39)
Prenatal Care Visits (≤ 3)	1.39 (1.23 – 1.58)	1.39 (1.23 – 1.58)	1.39 (1.23 – 1.58)
Pre-existing Diabetes	1.27 (0.99 - 1.64)	1.27 (0.99 - 1.64)	1.27 (0.99 - 1.64)
Pre-pregnancy weight (≥ 75kg)	1.48 (1.43 - 1.54)	1.49 (1.43 - 1.56)	1.56 (1.48 - 1.65)
Level 1 = never smoked, Level 2 = light smoker, Level 3 = moderate smoker, Level 4 = heavy smoker.			

4.0 Discussion

The results of this large population-based study support that smoking during pregnancy is a modifiable dose-dependent risk factor of adverse fetal growth that also has a strong relationship with other risk behaviour and low SES indicators. Compared to all lower levels of smoking, heavy smokers (≥ 10 cigarettes/day) had substantially worse birth outcomes and were also at increased risk to be identified for alcohol use and drug use, be a single parent, attended fewer prenatal care visits and have pre-pregnancy weight greater than 74 kilograms. Although the addition of a major SES variable, level of education, was limited to only 10% of our study population, the main effects and general trends were corroborated. Heavy smokers were 3.8 times more likely to have not graduated high school compared to moderate, light and non-smokers combined supporting the possibility that reports of smoking greater than ten cigarettes per day might be an early marker for the need for comprehensive supports to reduce adverse outcomes.

The adjusted ORs for the impaired fetal growth outcomes (SGA, IUGR and term-LBW) were nearly twice the magnitude between heavy and light smokers. The addition of the education variable into the logistic models attenuated the effect of light smokers to the degree of no significant difference between light, former and never smokers while the effect of moderate and heavy smoking remained relatively stable with roughly double the risk. The effect of smoking on PTB was completely removed after adjusting for maternal education. This suggests that while behavioural and SES indicator variables, particularly maternal education, explain some or all of the risk attributed to light smoking, heavy smoking remains a robust marker of increased risk for the impaired fetal growth outcomes. Whether this observed effect is strictly biological or is partially a marker for some latent unmeasured risk factor, heavy smoking readily identifies approximately five percent of the BC population who could benefit from additional support services. These results were consistent with findings from a population-based study from Nova Scotia [21] as well as a prospective cohort study that used anthropometric ultrasound measurements to compare fetal growth in smoking and non-smoking expectant mothers [22].

The mechanisms to which cigarette smoke exposure effects fetal growth is not completely understood; however, IUGR correlates with defects in placental transport and metabolism functions which seems to restrict nutrient supply [23]. Zdravkovic et al. report that constituents in cigarette smoke directly affect placental cytotrophoblast proliferation and differentiation which reduces blood flow and creates a hypoxic environment [24]. Using a mouse model, Detmar et al. found that polycyclic aromatic hydrocarbons (PAHs), a main component in cigarette smoke, caused IUGR in the fetuses of exposed dams and yielded alterations in placental vascularisation with significantly reduced arterial surface area and volume [25]. PAHs are also a main constituent of vehicular exhaust, particularly diesel, and there is mounting evidence of an association between said pollutant and growth restricted birth outcomes [26, 27].

The results from the pp-odds model show that most of the covariate risk factors primarily predict maternal smoking in general versus non-smokers. Variables such as single parent, drug and alcohol indication and young maternal age were significant across all levels comparison, but had the strongest effects in comparing non-smokers to all other levels of smoking. Conversely, parity exhibited its strongest effects in the third comparison (heavy smokers versus never, light, and moderate smokers combined). This suggests that while being multiparous is a marker for maternal smoking in general, it predicts heavy

smoking versus moderate or light smoking habits. A similar observation was found in a study of UK women regarding gravida and smoking behaviour in subsequent pregnancies, commenting on the double exposure of the previous children to cigarette smoke both pre- and postnatally [28]. While older maternal age was associated with having reported 'never smoked', older mothers who did smoke were more likely to be heavy smokers. This trend of older mothers being heavy smokers was also observed in the Nunavut chart review study [12].

The results for the pp-odds model including maternal education generally hold true to the first model. The effects for age, parity, single parent, drug flag, and alcohol flag are slightly attenuated but remain significant with the same trend. Education (no grade 12) had a strong constant effect on maternal smoking across all levels of comparison, suggesting an important role in health literacy. Maternal level of education has been shown to be a powerful determinant of perinatal health, independent of, and stronger than that of neighbourhood income [29]. Having low maternal educational attainment, being young and a single parent are indicators of low socio-economic status that may exert additional stress on the pregnancy. The biochemical response to stress via elevated basal cortisol levels has been associated with low birth weight [30]. Three major systems are thought to be involved in the biological pathway linking maternal mental health and stress with adverse birth outcomes which include the neuroendocrine, the immune/inflammatory, and the cardiovascular systems with placental corticotrophin releasing hormone playing a central coordinating role [31]. Indicators of women's mental health during pregnancy such as psychosocial stress, level of social and financial support and depression may be one possible pathway to which low SES is associated with adverse birth outcomes.

The majority of results from this British Columbia based study were consistent with recent findings from Norway [32], Germany [33], and a national Canadian survey that analyzed the associated risk factors of smoking during pregnancy [8]. The Canadian study found that non-immigrant, single parent, low household income, no/little prenatal classes, less education, passive (i.e. partner) smoking, older maternal age and a higher number of stressful events were significantly associated with maternal smoking in general but did not assess quantity of cigarettes smoked [8]. An Australian study of similar design to our research also used registry data and found young maternal age, lack of antenatal care and low SES were associated with maternal smoking [34]. Both papers highlighted the importance of antenatal care as a critical access point to educate expectant mothers

regarding a healthy pregnancy. Importantly, the study from Australia found that first-time mothers and those who accessed prenatal care early in their pregnancies had an increased likelihood of smoking cessation [34].

The province of BC has a relatively healthy birthing population compared to the rest of Canada and has amongst the lowest rates of maternal smoking and exposure to 2nd hand smoke in Canada [35]. Further, BC has high grade 12 completion rates among pregnant women which likely influence the relatively low rates of risk behaviours such as maternal smoking. BC had lower rates of preterm birth and is around the Canadian average for rates of SGA. Despite these positive outcomes, the ability to recognize those at particular risk early in pregnancy and provide preventative programs could help achieve better outcomes for all expectant mothers. Specifically, our findings suggest that heavy maternal smoking will identify approximately five percent of women in BC at particular increased risk of adverse outcomes that may benefit from additional services to promote a healthy pregnancy. With respect to epidemiological analysis of population-based perinatal datasets, there is potential to use heavy maternal smoking as a proxy for unreliable or unmeasured individual-level behavioural and/or socio-economic data. Maternal self-reported smoking tends to be routinely collected for most birth registries making it an accessible variable compared to many other risk factor variables or when linkage to external data in not available.

There were several limitations to this analysis. First, there were no data on passive smoking rates (i.e. exposure to environmental tobacco smoke or having a partner who smokes), psychosocial stress, ethnicity, whether the pregnancy was planned, birth intervals for multiparous women, potential occupational exposures, or household income. Further, some of the covariates examined had high missing data. As described earlier, pre-pregnancy weight was missing approximately 25 percent of its values, and maternal education data were only available for 28,210 records (12%). The greatest concern when an important variable is poorly populated, is that the absence/presence of values is biased (i.e. are not missing at random). For instance, care providers may only be asking those individuals about their education status where literacy is a concern, and as a result the distribution would be biased and shifted to the left. Therefore missing data not only reduces the statistical power due to list-wise deletion (i.e. records with missing data are not used in that particular test), but also reduces the overall reliability of that variable and potentially the appropriateness of the model.

To address this potential bias, sensitivity analyses were carried out for level of education and pre-pregnancy weight. These tests demonstrated that records with missing education data tended to have small increased risks for all adverse birth outcomes and some maternal risk characteristics; while those missing pre-pregnancy weight data had mixed birth outcomes results but increased risk for most maternal characteristics. However, the overall age structure and cigarette consumption between those with and without missing data were nearly identical with similar medians and inter-quartile ranges. Taken as a whole, these results suggest that the missing education and pre-weight data may result in underestimating the risk of some adverse birth outcomes but the degree of missing data is relatively consistent across the levels of smoking and therefore it would be predicted not to affect the observed general trends of our analyses. Further, a review of the mean number of years of education for the Canadian female population (age 25-36) fall within the mean and standard deviation of our maternal years of education variable, 14.2 versus 13.9 ± 2.6 [36]. However, given the strong association between maternal education, smoking and risk of adverse outcomes, these results reinforce the importance for the standardized and complete collection of SES variables for *all* patients by all prenatal health care providers.

Another potential limitation is the self-reporting bias of cigarette consumption. Self-reported smoking status among pregnant women is susceptible to bias, and may lead to attenuation of the true effect of smoking on birth outcomes [37]. Rates of misclassification in the United States using data collected from the National Health and Nutrition Examination Surveys (NHANES) estimated non-disclosure to be around 20 percent [38]. The rate of misclassification was consistent with other studies [39], as was the demographic predictors of non-disclosure. Many studies used serum, salivary, or urinary cotinine as a biomarker to assess the degree of non-disclosure in smoking status, and have found a range of between 13-25 percent depending on the cut-off values used to classify one as an active smoker. Non-disclosure was higher among those who reported they were former smokers, and younger maternal age (20-24). The stigma around maternal smoking may lead some respondents to under report their actual consumption habits. Possible recall bias can also be assumed given the peaks in the histogram (Figure 11) corresponding at multiples of 5. This could be due to responses given in terms of some fraction in packs of cigarettes per day, such that half a pack is equal to ten cigarettes. None the less, our results suggest that *reported* number of cigarettes smoked correlates with adverse birth outcomes and

associated socio-economic risk factors suggesting the information as provided will help identify those at highest risk.

Future analyses may include running a hierarchical multilevel model with the inclusion of neighbourhood-level deprivation scores to determine if clustering of observations by neighbourhoods regarding birth outcomes, smoking rates or prenatal care attendance. This type of analysis would be useful as a baseline to further study the effect of local air pollution exposure measured at the neighbourhood-level on birth outcomes and the potential interactions with SES and other risk variables.

5.0 Conclusion

We have demonstrated that self-reports of heavy smoking (≥ 10 cigarettes/day) early in pregnancy could be used as a marker for latent or other often unmeasured lifestyle risk factors that influence birth outcomes. Heavy smokers had worse outcomes and were substantially more likely to demonstrate other risk factors compared to other levels of smoking. While strategies for smoking cessation are important and supported by our study, the underlying issues that lead to adverse birth outcomes might not be addressed with a narrow focus. This information may be used for planning targeted intervention programs not only for smoking cessation but potentially other maternal support services such as nutrition and healthy pregnancy education with the overall goal of optimizing birth outcomes.

6.0 References

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Chapter 4: The reduction of birth weight by fine particulate matter and its modification by maternal and neighbourhood-level factors: a multilevel analysis in British Columbia, Canada

Erickson A.C., Ostry A, Chan L.H.M., Arbour L. The reduction of birth weight by fine particulate matter and its modification by maternal and neighbourhood-level factors: a multilevel analysis in British Columbia, Canada. *Environmental Health*; 2016 Apr 14; 15(1).

Abstract

Background: The purpose of this research was to determine the relationship between modeled particulate matter ($PM_{2.5}$) exposure and birth weight, including the potential modification by maternal risk factors and indicators of socioeconomic status.

Methods: Birth records from 2001 to 2006 (N=231,929) were linked to modeled $PM_{2.5}$ data from a national land-use regression model along with neighbourhood-level SES and socio-demographic data using 6-digit residential postal codes. Multilevel random coefficient models were used to estimate the effects of $PM_{2.5}$, SES and other individual and neighbourhood-level covariates on continuous birth weight and test interactions. Gestational age was modeled with a random slope to assess potential neighbourhood-level differences of its effect on birth weight and whether any between-neighbourhood variability can be explained by cross-level interactions.

Results: Models adjusted for individual and neighbourhood-level covariates showed a significant non-linear negative association between $PM_{2.5}$ and birth weight explaining 8.5% of the between neighbourhood differences in mean birth weight. A significant interaction between SES and $PM_{2.5}$ was observed, revealing a more pronounced negative effect of $PM_{2.5}$ on birth weight in lower SES neighbourhoods. Further positive and negative modification of the $PM_{2.5}$ effect was observed with maternal smoking, maternal age, gestational diabetes, and suspected maternal drug or alcohol use. The random intercept variance indicating between-neighbourhood birth weight differences was reduced 75% in the final model, while the random slope variance for between-neighbourhood gestational age effects remained virtually unchanged.

Conclusion: We provide evidence that neighbourhood-level SES variables and $PM_{2.5}$ have both independent and interacting associations with birth weight, and together account for 49% of the between-neighbourhood differences in birth weight. Evidence of effect modification of $PM_{2.5}$ on birth weight across various maternal and neighbourhood-level

factors suggests that certain sub-populations may be more or less vulnerable to even relatively low doses $PM_{2.5}$ exposure.

1.0 Background

Studies of exposure to particulate air pollution have consistently shown an association with low birth weight, a predictor of fetal growth restriction and important determinant of infant and child wellbeing [1–3]. The fine fraction of particulate matter ($PM_{2.5}$ - less than 2.5 microns) is a complex mixture of elemental and organic carbon compounds, metals and gases that stem predominantly from vehicle exhaust, residential heating and industrial emissions. $PM_{2.5}$, which includes ultrafine particles less than 0.1 microns, can penetrate deep into the pulmonary alveolar tissue where inflammatory mediators and possibly the particles themselves translocate into the bloodstream causing systemic cardiovascular and immunological alterations such as platelet activation, coagulation and endothelial dysfunction [4–6].These physiological changes extend to the placenta, a highly vascularized organ and extension of the maternal cardiovascular system with similarly affected endothelial cellular tissues particularly susceptible to oxidative and inflammatory injury [7–9]. Excess or uncontrolled oxidative stress and inflammation early in pregnancy may disrupt placental cell growth and differentiation potentially leading to deficient deep placentation and morphological adaptations associated with several adverse pregnancy outcomes including fetal growth restriction [10].

These mechanisms by which $PM_{2.5}$ may act to adversely impact the reproductive system are not fully understood; however, evidence supports the potential for a shared mode of developmental toxicity with several other known risk factors [5,11]. This includes factors that also promote or are associated with oxidative stress and inflammation such as smoking [12], drug use [13], advanced maternal age [14] and gestational diabetes[15], and low socioeconomic status (SES) in general [16]. The causal pathways in which SES contributes to adverse pregnancy outcomes can be conceptualized in terms of 'downstream' or mediating exposures, stresses and behaviours acting on the individual through 'upstream' society-level determinants such as poverty, poor education, income inequality and social discrimination/marginalization over the lifespan [17,18]. This impact of the social environment on health behaviours and outcomes creates hierarchical structures within which individuals are nested in neighbourhoods and communities with their own set of attributes that can promote or antagonize health and healthy behaviours [19,20].

A particular challenge in environmental epidemiology is handling data at differing geographic scales. Birth registries and vital statistics provide data on individual births and certain risk factors, but may not have data on socially patterned risk factors. Alternatively, reliable SES data such as education, income and housing quality are often only available from national census databases using arbitrary administrative spatial units. Finally, obtaining individual-level environmental exposure data is often not possible. Therefore, the epidemiologist is often left with a mix of individual-level observations clustered within neighbourhood areas each with distinct attributes. The use of multilevel statistical models separate the individual-level effects from the context of their social and physical environments and can therefore quantify the degree of clustering of individuals within neighbourhood areas and test whether neighbourhood factors themselves have direct effects on the health outcome or act indirectly via the modification of individual-level variables [21,22].

Through the mechanisms of oxidative stress and inflammation there is evidence that SES may not only confound but modify the $PM_{2.5}$-birth outcome relationship [23–25]. Various exposures and experiences may act in a non-additive manner to influence fetal development [5]. We present a multilevel cross-sectional analysis of the association between birth weight and $PM_{2.5}$ in British Columbia, Canada where levels of $PM_{2.5}$ are relatively low but can vary substantially between different communities [26]. We explore the potential for between-neighbourhood variability for the slope of gestational age on birth weight and whether interactions with $PM_{2.5}$, neighbourhood-level SES indicators, and/or individual-level risk factors are able to explain any neighbourhood-level variability. We had three research questions: 1) does exposure to $PM_{2.5}$ and residence in low SES neighbourhoods in BC have significant independent negative associations with birth weight; 2) does the effect of gestational age on birth weight differ by neighbourhoods; and 3) does $PM_{2.5}$ interact with neighbourhood-level SES and/or individual-level risk factors to modify their independent effects on birth weight to help explain any neighbourhood-level differences.

2.0 Data and Methods

This was a population-based retrospective cohort of singleton births in British Columbia from 2001 to 2006 (N=237,470). Data from the BC Perinatal Data Registry were provided by Perinatal Services British Columbia (PSBC) which included information on maternal-infant health status and outcomes, reproductive history, maternal risk factors,

attributes and residential postal codes. The Registry accounts for 99% of births and stillbirths in BC of at least 20 weeks gestation or at least 500 grams birth weight. Research data access is provided by a Partnership Accord /Memorandum of Agreement between all BC Health Authorities and PSBC through the *Freedom of Information and Privacy Protection Act* [27]. Research ethics board approval was granted by the University of Victoria (ethics protocol #: 11-043).

The outcome variable was continuous birth weight of singleton births. In order to avoid potential selection bias, we included all births (stillbirth and live) for all gestational ages (20-42 weeks). Excluded records included out-of-province and invalid postal codes (n=1,096), non-viable births prior to 20 weeks gestation or 500 grams (n=14), and the list-wise deletion of births missing important data including: cigarettes smoked per day (cigarettes/day, n=2,501), $PM_{2.5}$ (n=1,510), gestational age (n=373) birth weight (n=41). All continuous variables, except cigarettes/day, were standardized and centered to ease interpretation and aid model convergence.

The spatial location of each birth record was geocoded based on the latitude-longitude coordinate of the mother's residential postal code at the time of delivery using *GeoRef* [28]. Birth records were related to their corresponding census dissemination area (DA) by performing a point-in-polygon spatial join procedure in *ArcGIS 10.2* [29]. DAs are the smallest geographical unit for which census data are available and represent neighbourhood blocks ranging between 200–800 people. While DAs do not necessarily represent existing neighbourhood communities [30], they can act as proxies for a general catchment area of personal home-life activities [31,32]. Birth records were identified as being either rural or urban using the Statistics Canada Metropolitan Influence Zone (MIZ) codes which are based on commuting flows of small towns into larger cities and metropolitan areas [33].

Exposure to $PM_{2.5}$ was estimated using a national land-use regression (LUR) model developed to estimate $PM_{2.5}$ at the census street block-face level [34]. The model used a number of predictors including satellite measures, proximity to major roads and industry to account for 46% of the variability in measured annual $PM_{2.5}$ concentrations. Unlike nitrogen dioxide (NO_2), $PM_{2.5}$ tends to have a more homogeneous intra-urban distribution between personal, indoor and ambient [35]. The LUR model estimates used for this study showed very little variability of $PM_{2.5}$ exposures between individuals within a given DA. We

therefore aggregated the point-level estimates of $PM_{2.5}$ to their DA-level mean and related it to individual birth records as an area-level variable.

The DA-level SES and demographic data were represented by three related but independent datasets all based on the 2006 Statistics Canada national census. The first was a Canadian SES index (SESi) developed by Chan et al [36]. The second was an education variable representing the proportion of population over 15 with any post-secondary education, including college, trades, or university. The third was the proportion of continental Asian immigrants by DA as it's been shown in BC and elsewhere that healthy babies from Asian and South Asian backgrounds are constitutionally smaller compared to their Caucasian counterparts [37,38]. Asian and South Asian ethnicities are well-represented throughout BC but particularly in concentrated pockets throughout the major urban center of Metro Vancouver where levels of $PM_{2.5}$ are also high. The correlation between immigrant density with SESi and $PM_{2.5}$ was -0.62 and 0.53 respectively ($p<0.001$), we therefore created a residual immigrant density variable using a sequential regression technique [39]. Here, immigrant density was regressed against SESi and $PM_{2.5}$ with the saved residuals representing the uncorrelated and independent contribution of immigrant density on birth weight freed from its collinearity with SESi and $PM_{2.5}$. This same method was used between SESi and education ($r=0.25$) creating and residual education variable. The education and immigrant data were obtained by access to ABACUS via the Data Liberation Initiative [40].

In order to avoid data loss from rural DAs, imputation for missing SES, education and immigrant density values was performed. Taking advantage of the nested hierarchical structure of the administrative census and health boundaries, the mean value for a larger encompassing census subdivision (CSD) or local health area (LHA) was imputed for a nested DA with a missing value. There were 1,441 values imputed in 52 DAs for SESi (0.6% of final N, 0.8% of DAs), and 3,170 values imputed in 108 DAs for both education and immigrant density (1.4% of final N, 1.7% of DAs). Sensitivity analyses were performed using only the non-missing data.

Hierarchical (multilevel) linear regression models were used to test our research questions, thereby accounting for the clustering, or non-independence, of individuals (level-1) belonging to a given DA neighbourhood (level-2). The multilevel model allows the intercept and slope to act as random parameters having between-area (DA) variability from an overall (BC-wide) mean intercept and slope. That is, each DA has its own intercept and

slope in which their variability from the overall intercept and slope can be investigated with the addition of level-1 and level-2 variables and their interactions [41]. We followed a bottom-up approach to model building to quantify the explained proportional change in variance (PCV), the multilevel model equivalent to an R^2 [22]. We started with an empty (null) random intercept model without any independent variables in which birth weight is only a function of the mother's residential DA. The presence of significant random intercept variance indicates there are unexplained differences between neighbourhood means of birth weight. The proportion of the total variance in birth weight that arises due to neighbourhood differences can be quantified by computing the intra-class correlation (ICC), and hence provides the degree of clustering of individual birth weight within neighbourhoods [22].

Gestational age was added to the null model and given a random slope (i.e. the mean within-DA effect of gestational age was allowed to differ between DAs). The presence of a significant random slope indicates that its effect on birth weight is not constant (or equal) for all DAs. Subsequent models included the individual and DA-level variables along with cross-level and within-level interactions in order to assess their fixed effects on birth weight but to also determine if their inclusion addressed any unexplained intercept or slope variance. Models were tested using the Akaike Information Criterion (AIC) to evaluate model performance. All statistical analyses were conducted in *Stata 13IC* [42].

Finally, while multilevel models address *intra*-area dependence while quantifying *inter*-area variance, they assume spatial independence among neighbouring areas. However environmental and social processes can extend beyond arbitrary neighbourhood boundaries. Additionally as mentioned above, census DAs do not necessarily represent neighbourhood dynamics, services, infrastructure, etc.; and evidence of spatial clustering between DAs may indicate that an alternative neighbourhood areal unit should be considered. We used spatial methods to test for this by checking the level-1 model residuals and level-2 predicted random parameters (intercepts and slopes) for spatial autocorrelation using the local Moran's *I* statistic [43]. The presence of significant residual spatial autocorrelation indicates the existence of unobserved spatial processes causing DAs to cluster and is a sign of model misspecification. Prediction of the DA-level random intercept and slope errors used an Empirical Bayes method [44] available as a post-estimation command in *Stata 13IC*.

3.0 Results

After exclusions there were 231,929 singleton (live and stillborn) births located in 6,338 neighbourhood DAs (min. = 1, max. = 781, avg. = 37). Table 4 summarizes the untransformed individual and neighbourhood covariates (non-centered, non-standardized). Table 5 reports the adjusted coefficients for the individual and DA-level covariate fixed effects on continuous birth weight (Model 1 to 3). Gestational age was modeled using a quadratic term to account for the rapid fetal growth in mid-gestations and its slower growth post-term (>37 weeks). Maternal smoking (cigarettes/day) and $PM_{2.5}$ were also modeled using a quadratic terms, both indicating a subdued dose-response with increasing exposure.

Model 2 added the DA-level variables of SESi, education, immigrant density and rural residence. Their fixed effects show that lower SES and higher Asian immigrant density were significantly associated with lower birth weights (Table 5). Rural DAs and DAs with higher proportion of post-secondary education were not significantly associated with birth weight in this model. However, both became significant after the addition of $PM_{2.5}$ and season of birth (cold vs. warm) in Model 3. Higher education had a positive association with birth weight, while rural areas had a significant negative association with birth weight. $PM_{2.5}$ was found to have a significant non-linear negative association on birth weight whereby the negative effect tapers off at higher concentrations of $PM_{2.5}$ (Figure 13). Being born in a cold (fall-winter) month also had a significant negative association with birth weight (Table 5).

Table 4: Descriptive statistics# for individual (Level-1) and DA (Level-2) covariates

Variables Level-1 (individual)	Mean	Std.Dev.	Min-Max	$PM_{2.5}$ Mean (SE)[a] Absence / 1st quintile	 Presence / 5th quintile
Birth weight (grams)	3433.3	566.51	135-6475	7.30 (.016)	7.36 (.018)†[1]
Gestational age (weeks)	38.8	2.02	19-44	7.30 (.016)	7.30 (.017)[2]
Maternal age (years)	29.8	5.60	11-55	7.10 (.022)	7.39 (.014)†
Nulliparous	0.45	0.50	0-1	7.27 (.016)	7.34 (.016)†
Gestational diabetes	0.06	0.25	0-1	7.29 (.016)	7.53 (.016)†
Pre-existing diabetes	0.004	0.06	0-1	7.30 (.016)	7.34 (.034)
Gestational hypertension	0.02	0.15	0-1	7.30 (.016)	7.44 (.019)†
Poor prenatal care	0.09	0.29	0-1	7.28 (.016)	7.47 (.02)†
Drug/Alcohol flag	0.02	0.15	0-1	7.31 (.016)	7.08 (.026)†
Cigarettes/day	0.79	2.91	0-20	7.33(.015)	7.02 (.023)†[3]
Fall/Winter season	0.48	0.50	0-1	7.29 (.016)	7.31 (.016)†
Level-2 (DA) Variables					
SESi	-0.08	0.58	-2.22 – 1.18	7.82 (.027)	6.95 (.032)†‡
Higher education	0.50	0.12	0 – 0.95	7.16 (.04)	7.53 (.022)†‡
Immigrant density	0.16	0.19	0 – 0.86	6.75 (.023)	7.95 (.021)†‡
Rural address	0.11	0.32	0 – 1	7.39 (.014)	6.59 (.061)†‡
$PM_{2.5}$ ($\mu g/m^3$)	7.30	0.86	4.41-10.23	--	--

values shown are unstandardized, non-centered; Poor Prenatal Care: having less than 4 prenatal care visits or was missing; Drug/Alcohol Flag: suspected possible use of illicit drugs or alcohol by health care provider; Cigarettes/day: self-reported number of cigarettes smoked daily at 1st prenatal visit (excluding non-smokers: 7.7 (5.41)); Fall/Winter Season: birth month = Sept – Feb; [a] robust standard errors adjusted for 6338 DA clusters; †significant difference at $p<0.05$ using Wald tests; ‡1st vs. 5th quintile; [1] normal birth weight vs. low birth weight; [2] term birth vs. preterm birth; [3] non-smoker vs. current smoker.

Table 5: Adjusted individual and DA-level fixed effects on continuous birth weight

Variables Level-1 (individual)	Model-1 β (95%CI)	Model-2 β (95%CI)	Model-3 β (95%CI)
Gestational age	310.2 (307.6 – 312.7)	308.7 (306.1 – 311.2)	308.5 (306.0 – 311.1)
Gestational age[a]	-11.6 (-12.2 – -11.1)	-11.9 (-12.4 – -11.3)	-11.9 (-12.5 – -11.4)
Maternal age	-6.6 (-8.6 – -4.7)	-6.0 (-8.0 – -4.0)	-4.7 (-6.6 – -2.7)
Nulliparous	-137.2 (-141.0 – -133.4)	-135.7 (-139.5 – -131.9)	-134.8 (-138.6 – -131.1)
Gestational diabetes	54.5 (47.1 – 61.8)	60.0 (52.7 – 67.4)	62.0 (54.6 – 69.4)
Pre-existing diabetes	320.7 (292.1 – 349.3)	320.6 (292.1 – 349.1)	321.2 (292.6 – 349.7)
Gestational hypertension	-90.1 (-102.3 – -77.9)	-88.9 (-101.0 – -76.7)	-87.6 (-99.7 – -75.4)
Prenatal care visits	-59.0 (-65.3 – -52.8)	-55.0 (-61.2 – -48.7)	-52.2 (-58.4 – -45.9)
Drug/Alcohol flag	-79.1 (-91.2 – -67.1)	-79.2 (-91.2 – -67.2)	-81.7 (-93.7 – -69.7)
Cigarettes/day	-20.8 (-22.5 – -19.0)	-22.0 (-23.8 – -20.3)	-22.7 (-24.4 – -20.9)
Cigarettes/day[a]	0.63 (0.51 – 0.74)	0.68 (0.57 – 0.79)	0.7 (0.59 – 0.82)
Fall/Winter season	––	––	-6.8 (-10.4 – -3.2)
Level-2 (DA)			
SESi	––	37.4 (35.2 – 39.7)	29.4 (27.0 – 31.8)
Higher education	––	-2.1 (-4.4 – 0.2)	3.0 (0.7 – 5.3)
Immigrant density	––	-29.2 (-31.4 – -26.9)	-31.3 (-33.5 – -29.1)
Rural address	––	4.8 (-3.4 – 12.9)	-14.6 (-22.6 – -6.7)
$PM_{2.5}$	––	––	-23.9 (-26.5 – -21.3)
$PM_{2.5}$[a]	––	––	2.8 (1.3 – 4.3)

See Table 4 legend for variable definitions; [a] Variables were modeled as quadratics.

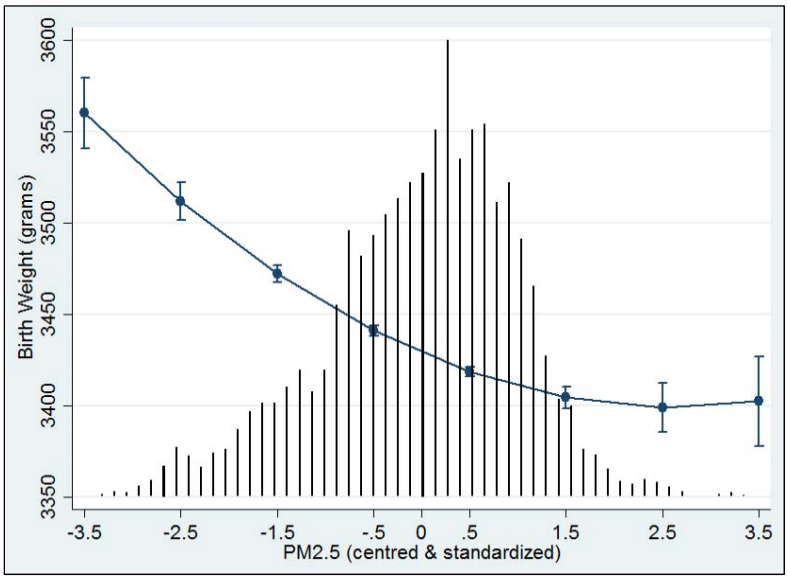

Figure 13: Adjusted Predicted Effects of $PM_{2.5}$ on Birth Weight

Predicted effects of $PM_{2.5}$ on birth weight with 95% confidence intervals are conditional on model covariates included in Model 4. Black vertical lines represent the frequency distribution of $PM_{2.5}$.

Model 4 tested interactions with $PM_{2.5}$ including cross-level (level-1 by level-2) and level-2 by level-2 interactions to explain the between-DA random intercept variability. The model results are presented in Table 6 including the main effects as well as the interaction effects with $PM_{2.5}$. Four maternal variables showed effect modification with $PM_{2.5}$ on birth weight. Maternal smoking and suspected drug or alcohol use both had positive interactions with $PM_{2.5}$ on birth weight revealing a subdued association with increased $PM_{2.5}$ exposure (Figure 14A and 14B respectively). Maternal age was also modified by differences in $PM_{2.5}$ exposure with younger maternal ages showing a larger reduction in birth weight with increased $PM_{2.5}$ exposure (Figure 14C). Alternatively, gestational diabetes was associated with a much greater reduction in birth weight with increasing $PM_{2.5}$ compared to normal births, essentially nullifying the higher birth weights produced by the condition (Figure 14D). Three DA-level variables showed significant effect modification with $PM_{2.5}$ on birth weight. First, the interaction between SESi and $PM_{2.5}$ revealed a more pronounced effect of $PM_{2.5}$ in lower SES neighbourhoods (Figure 15A). Higher Asian immigrant density buffered the $PM_{2.5}$ effect (Figure 15B), while rural DAs showed an additional reduction in birth weight with increasing $PM_{2.5}$ levels compared to urban DAs (Figure 15C).

The random effects, the explained proportional change in variance (PVC), and model diagnostics are presented in Table 7. The unadjusted ICC for the Null random intercept model was 0.019, indicating that 1.9% of the total residual differences in birth weight are attributable to DA-level contextual factors. With the inclusion of the level-1 covariates along with the random slope for gestational age the ICC_{adj}, now conditional on mean-centred gestational age (i.e. 38.8 weeks), increased to 2.3%. This was due to the large reduction in the level-1 residual variance (560.5 to 435.2) relative to the reduction in the level-2random intercept variance (78.8 to 67.0). The addition of DA-level variables in Model 2 and Model 3 removed a lot of the DA-level variance reducing the ICC_{adj} to 1.1% and 0.8% respectively.

Table 6: Adjusted individual and DA-level fixed effects on continuous and term birth weight and their modification by $PM_{2.5}$ (Model-4)

Variables	Main Effect β (95%CI)	Modification by $PM_{2.5}$ β (95%CI)	Corresponding Figure
$PM_{2.5}$[a]	-22.4 (-25.2 – -19.7)	4.9 (3.2 – 6.7)	1
Cigarettes/day[a]	-22.0 (-23.8 – -20.2)	2.8 (2.2 – 3.4)	14A
Drug/Alcohol flag	-80.6 (-93.0 – -68.2)	15.3 (4.4 – 26.2)	14B
Maternal age	-4.2 (-6.2 – -2.2)	5.5 (3.7 – 7.4)	14C
Gestational diabetes	70.2 (62.6 – 77.8)	-33.8 (-41.9 – -25.8)	14D
SESi	30.2 (27.7 – 32.7)	4.6 (2.0 – 7.2)	15A
Immigrant density	-33.3 (-35.8 – -30.7)	6.3 (3.3 – 9.2)	15B
Rural address	-29.1 (-39.1 – -19.1)	-16.4 (-24.5 – -8.3)	15C
Term Births, excluding stillbirths and congenital anomalies (N = 207,405)			
$PM_{2.5}$[a]	-24.1 (-26.9 – -21.2)	5.0 (3.2 – 6.8)	--
Cigarettes/day[a]	-21.9 (-23.8 – -20.0)	2.8 (2.2 – 3.4)	--
Drug/Alcohol flag	-80.1 (-93.6 – -66.6)	13.2 (1.2 – 25.2)	--
Maternal age	-3.1 (-5.2 – -1.1)	5.0 (3.1 – 6.9)	--
Gestational diabetes	60.2 (52.1 – 68.4)	-30.7 (-39.2 – -22.1)	--
SESi	30.5 (27.9 – 33.1)	4.3 (1.5 – 7.0)	--
Immigrant density	-36.0 (-38.7 – -33.3)	6.9 (3.8 – 9.9)	--
Rural address	-31.2 (-41.6 – -20.8)	-16.9 (-25.3 – -8.5)	--

[a] Modeled as a quadratic, Cigarettes/day: 0.7(0.6 – 0.8); Model adjusted for gestational age, nulliparous, diabetes mellitus, gestational hypertension, prenatal care visits, season of birth, DA-level education.

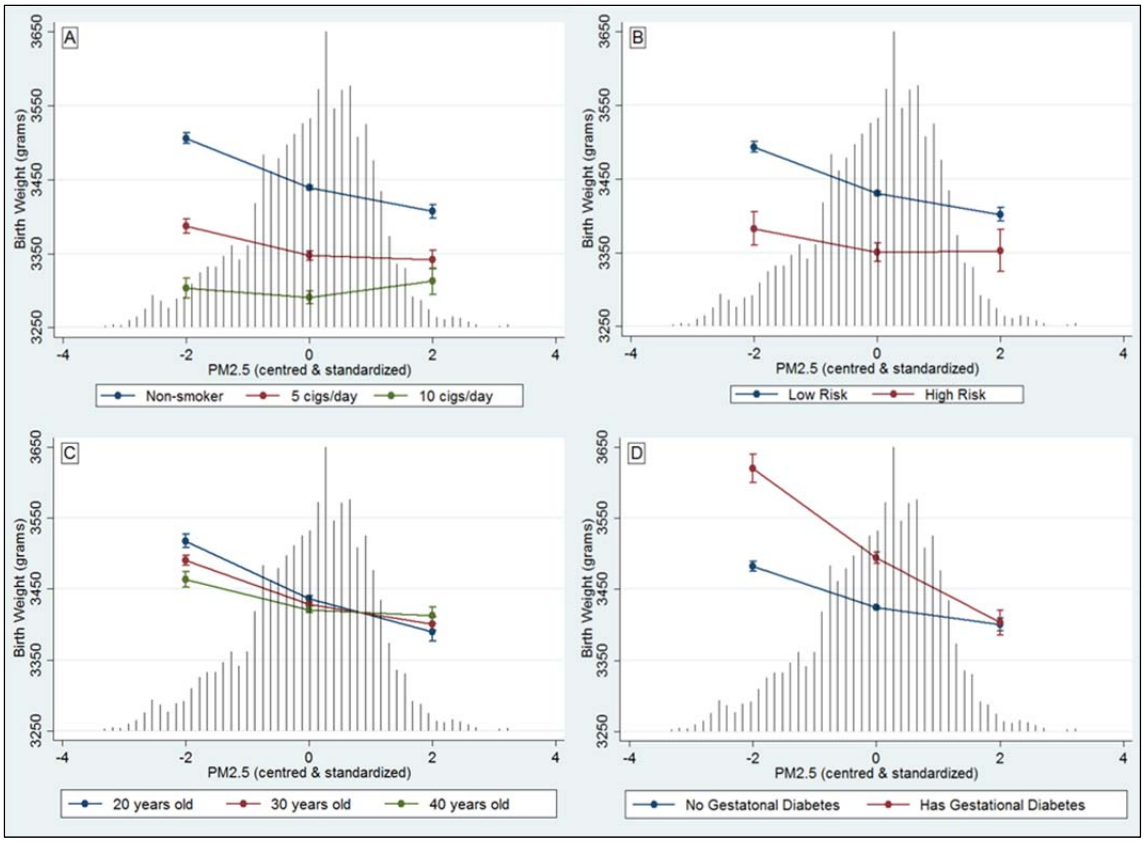

Figure 14: Adjusted Predicted Effects of maternal risk factors on birth weight across levels of $PM_{2.5}$

(A) Maternal Smoking (B) Suspected Drug or Alcohol Use (C) Maternal Age
(D) Gestational Diabetes. Predicted effects on birth weight with 95% CIs are conditional on model covariates included in Model 4. Black vertical lines represent the frequency distribution of $PM_{2.5}$.

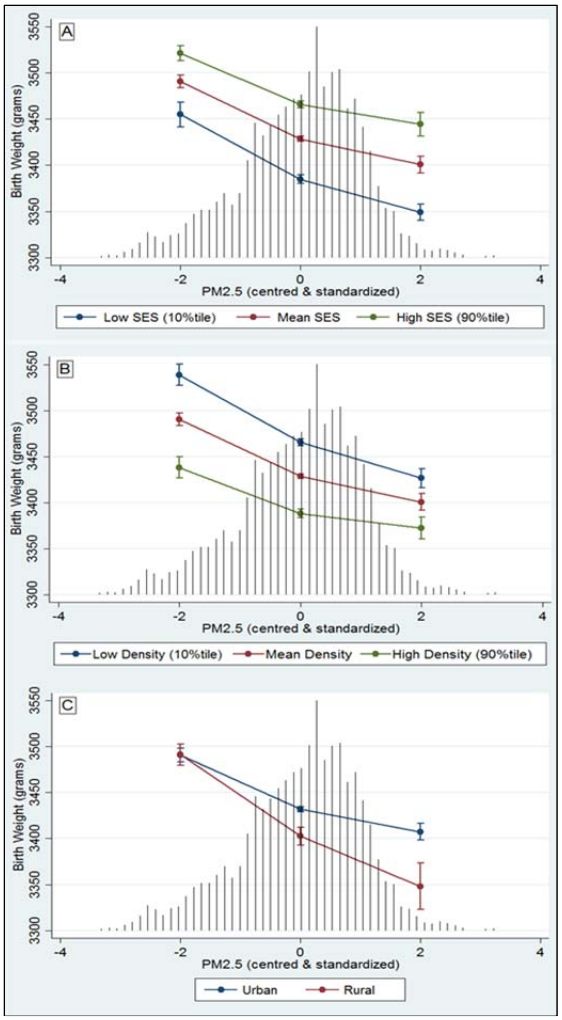

Figure 15: Adjusted Predicted Effects of DA-level factors on Birth Weight across levels of $PM_{2.5}$
(A) Socioeconomic Status Index (SESi) (B) Asian Immigrant Density (C) Rural Residence. Predicted effects on birth weight with 95% CIs are conditional on model covariates included in Model 4. Black vertical lines represent the frequency distribution of $PM_{2.5}$.

The level-2 random intercept standard deviation indicates that the mean birth weight for every DA has a degree of variability from the overall (BC-wide) mean birth weight. For the Null model, the overall birth weight intercept is 3,434.2 grams with a standard deviation of 78.8 giving an 8.6% difference in range between 95% of the DAs (3,434.2 ± (1.96 x 78.8) = 3,280.0 and 3588.8 grams). Similarly, we calculate the between-DA 95% distributional range of slopes for gestational age to fall between 255.8 and 361.6 grams (308.7 ± (1.96 x 26.6)), a 29.3% difference in how one week gestation increases birth weight between DAs.

Table 7: Random effects and model diagnostics from hierarchical linear models for continuous birth weight in BC, Canada

Random Effects & Model Diagnostics	Null Model	Null + r.slope	Model-1 (level-1)	Model-2 (SES)	Model-3 ($PM_{2.5}$)	Model-4 ($PM_{2.5}$ interact)
Variance Components						
L1 residual (sd)	560.5	442.9	435.2	435.3	435.3	435.1
L2 intercept (sd)	78.8	67.6	67.0	45.9	39.7	37.9
L2 slope (sd)	--	30.1	26.6	27.0	27.2	27.4
Intercept	3434.2	3448.4	3524.2	3521.3	3523.4	3522.6
AIC	597007	489148	480867	479403	478997	478753
L1-PCV (%)	Ref	37.5	39.7	39.7	39.7	39.7
L2-PCV (%)	Ref	26.4	27.7	66.0	74.5	76.8
ICC/VPC [#]	0.019	0.023	0.023	0.011	0.008	0.008
L1 Moran's $I^{\times}$	0.122	0.108	0.105	0.043	0.022	0.018
L2ri Moran's $I^{\times}$	0.300	0.301	0.310	0.113	0.079	0.071
L2rs Moran's $I^{\times}$	--	0.018	0.018	0.018	0.017	0.017

L1: level-1 = individual-level; L2: level-2 = DA-level; sd: standard deviation; AIC: Akaike Information Criterion; PCV: proportional change in variance; [#]ICC: Intra-class correlation – is called the VPC (variance partition coefficient) when conditional on the random-slope variable, thus values in table represent intercepts for individuals with mean gestational age (~39 weeks); L2ri: level-2 random intercept; L2rs: level-2 random slope; [×]all results were significant $p<0.05$ with 999 permutations using a queen criterion spatial weight matrix.

The level-1 and level-2 explained PCV (L1-PCV & L2-PCV) summarizes the relative degree of explained variance at the different levels between the different models. Using the Null model as the reference, the L1-model resulted in an L1-PCV & L2-PCV of 39.7% and 27.7% respectively (Table 7). These are fairly large PCVs, indicating the within and between-DA variance in birth weight shown in the Null model was moderately attributable to these individual (level-1) compositional factors, largely gestational age. The addition of the DA-level variables in Model 2 explained an additional 38.3% of the DA-level variance (cumulative L2-PVC = 66%). The additions of $PM_{2.5}$ and season of birth in Model 3 further explained an additional 8.5% of the level-2 intercept variance beyond that of Model 2. Model 4 accounted for an additional 2.3% L2-PCV.

Spatial analyses were used as a model diagnostic to test for significant spatial autocorrelation of the model residuals. The local Moran's *I* statistics reported in Table 7 indicate the degree of local spatial autocorrelation (i.e. spatial clustering) of the level-1 (L1) residuals as well as the level-2 predicted random intercepts (L2ri) and slopes (L2rs) for all five models. Interpreted in a similar manner as a regular correlation coefficient, the Moran's *I* statistic reveal the existence of significant localized clustering of residuals at both level-1 and level-2 in the Null and level-1 model. The addition of level-2 variables reduced the Moran's *I* substantially; however small but significant clustering remained.

Sensitivity analyses using only the non-imputed DAs (N_1=228,765 in 6,230 DAs) showed very minor differences in magnitude of significant variables in the birth weight models. In a second sensitivity analysis, we restricted the sample to only term births excluding stillbirths and congenital anomalies. As expected, there was a large reduction in the random-slope variance for gestational age due to dropping preterm births but no other differences in the observed relationships (Table 6, bottom half).

Finally, a check for potential collider bias was performed by omitting gestational age as a covariate from the models [45]. Random intercept models equivalent to those presented in Tables 5 and 6 were run and assessed for differences. Many of the individual-level covariate returned to resemble their unadjusted estimates listed in Table 4. The interaction between $PM_{2.5}$ and cigarettes/day remained unchanged, whereas the $PM_{2.5}$ interaction with drug or alcohol flag was no longer significant (p=0.066). The interaction between gestational diabetes and $PM_{2.5}$ was reduced by half, but was still significant. The effects of the DA-level variables SESi and immigrant density increased moderately beyond their 95% CIs listed for Model 4. The effect for $PM_{2.5}$ decreased but was still significant (-18.0 (95%CI -21.3 - -14.7)). The DA-level interaction between $PM_{2.5}$ immigrant density was reduced by half and marginally not significant (p=0.051), while the interaction between SESi and $PM_{2.5}$ was also reduced to non-significance (p=0.33).

Additional Tables and Figures of model results and diagnostics are available in Appendix 2. Results and interpretation regarding the other measures of impaired birth weight (SGA, tLBW, and IUGR) and preterm birth are available in Appendix 3.

4.0 Discussion

This study employed multilevel random coefficient models to assess the effect of $PM_{2.5}$ on birth weight and testing its interaction with individual and neighbourhood-level risk factors. Our results show that individual and neighbourhood-level factors are capable of modifying the association between $PM_{2.5}$ exposure and fetal growth. Furthermore, through the use of random-slopes models we show that the effect of gestational age on birth weight can vary considerably between neighbourhood DAs which was only moderately addressed in our models. After adjusting for individual-level covariates and DA-level socio-economic and socio-demographic variables, we found a significant non-linear effect between $PM_{2.5}$ and birth weight in 231,929 births in British Columbia, Canada. This association was robust to the exclusion of stillbirths and congenital anomalies as well as the

use of only term births and models dropping gestational age as a covariate, demonstrating that selection bias does not affect the observed results.

Our results corroborate the growing literature supporting a negative association between $PM_{2.5}$ and birth weight [3,46,47]. Even in settings of relatively low air pollution exposure similar to our study, significant reductions in birth weight have been observed [48]. This strengthens the evidence of the low-dose effects of $PM_{2.5}$ and is exemplified by Figure 13 which shows the largest potential effects on birth weight are seen at the low to mid concentrations of $PM_{2.5}$, a not uncommon dose-response phenomenon also observed in other exposure-disease contexts [49]. Other studies testing for non-linear effects of traffic-related air pollutants on fetal growth have been mixed [23,50,51]. Interestingly, we found a similar non-linear dose-response between cigarettes/day and birth weight, an effect also shown by England et al using both self-reported cigarettes/day as well as urine-cotinine levels to assess exposure [52].

Our results show a negative interaction between $PM_{2.5}$ and SES such that a more pronounced effect of $PM_{2.5}$ was seen in lower SES neighbourhoods (Figure 15A). We also observed significant interactions between $PM_{2.5}$ and Asian immigration density as well as with $PM_{2.5}$ and living in a rural location (Figure 15B and 15C respectively). This suggests that that not only can neighbourhood characteristics influence fetal growth but can also modify exposures either positively or negatively. The biological mechanisms supporting such interactions have been recently reviewed [5], and have been indirectly supported in epidemiological studies that found stronger effects of $PM_{2.5}$ across race, age and SES groups [23,25,53]. For example, the observed lower birth weights associated with neighbourhoods with higher densities of continental Asian immigrants is likely due to constitutional birth size differences [37,38], but the positive interaction with $PM_{2.5}$ may reflect the buffering effect of strong community cohesiveness and beneficial cultural practices [23,32]. A similar interaction was found by Basu et al in which births to Asian mothers exhibited smaller birth weight reductions for $PM_{2.5}$ constituents compared to Caucasian births [23]. However, similar interactions were not found by Currie et al between traffic-related CO exposure and risk factors such as race, education, or low income [54].

The significant negative interaction between rural address and $PM_{2.5}$ may reflect the underestimation of $PM_{2.5}$ in rural areas by the LUR model [34]. The composition of $PM_{2.5}$, and thus its relative toxicity, is shown to vary spatially depending on its source (e.g. wood smoke vs. traffic-related emissions) and may partially explain the observed rural-urban

differences [4,6]. The significant negative association between season of birth and birth weight could also reflect the increased presence of wood heating and vehicle exhaust in combination with winter stagnation events, but could also reflect a change in diet or increased infection rates [4,55]. An interaction between season of birth and $PM_{2.5}$ was not statistically significant.

Interactions between $PM_{2.5}$ and maternal-level variables shown to reduce birth weight independently revealed some counter-intuitive results. This included the $PM_{2.5}$ interaction with maternal smoking (cigarettes/day) and with suspected drug/alcohol use where increasing $PM_{2.5}$ levels tempered the negative effect of these risk factors (Figure 14A and 14B). This finding was counterintuitive to our original hypothesis and published literature [54], and gave rise to the suspicion of survival bias due to competing risks (i.e. risk behaviours leading to early miscarriage, preterm or stillbirths). Although we were not able to control for fetal loss prior to 20 weeks gestation, survival bias was mitigated by using a near full population sample that included stillbirths, congenital anomalies and preterm births. Furthermore, the positive interaction between maternal smoking and $PM_{2.5}$ was unchanged after the sensitivity analyses using only term births as well as for potential collider bias; whereas the interaction between drug and alcohol use and $PM_{2.5}$ remained positive but was no longer significant ($p=0.054$) [45]. The persistence of this finding leads to a hypothesis that some individual-level exposures may act as a pre-conditioning stress that activates an adaptive response of increased biological resistance to similar or other stressors [56].

A protective effect of older maternal age against $PM_{2.5}$ exposure was also observed by Basu et al [23], and may stem from increased nutritional awareness among older women and/or more secure income and support networks thereby reducing potential stress and anxiety [57,58]. Currie et al also found significant interactions between traffic-related carbon monoxide exposure and maternal age, but that both younger (< age 19) and older (> age 34) maternal age had greater reductions in birth weight [54]. Gestational diabetes has been shown to be associated with $PM_{2.5}$ and other air pollutants [59,60]; however, their interaction with respect to birth weight has not been assessed. Our study showed that pregnancies affected by gestational diabetes had significantly higher birth weights as expected but revealed a sharp reduction in birth weight with increasing $PM_{2.5}$. This significant negative interaction between $PM_{2.5}$ and gestational diabetes could be related to

excess of systemic or placental oxidative stress and inflammation resulting in restricted fetal growth [15,61].

While the application of multilevel models in perinatal epidemiology have become more common [62], most have been random intercept models with very few including a random-slope parameter. Permitting the slope for individual-level gestational age to be random can elucidate how its effect on birth weight differs between DAs. For example, the addition of level-1 covariates reduced the random-slope variability from 30.1 to 26.6. This suggests that that these maternal risk factors act through gestational age to influence birth weight and are not distributed homogeneously across DAs. In light of these findings, significant inter-DA variance remained for both the random intercept and slope. In other words, despite explaining a substantial proportion of the between-DA variance in birth weight with both level-1 compositional and level-2 contextual factors, there remained unmeasured DA-level mechanisms acting either directly on fetal growth and/or through gestational age to produce between neighbourhood differences in birth weight.

Spatial analyses were used to examine the wider spatial context within which the DAs are situated as well as a serving as a measure of model specification and how well the chosen representative neighbourhood (DA) unit performed. The inclusion of the DA-level variables and interactions substantially reduced the spatial autocorrelation in the level-1 and level-2 random intercept residuals (L1 & L2ri Moran's *I* in Table 7). There was very little spatial autocorrelation in the level-2 random-slope parameters (L2rs Moran's *I*), but was also slightly reduced in the DA-level models. Although very small, significant spatial autocorrelation remained in the residuals, particularly for the random intercept, which could bias the model standard errors and increase the risk of making Type I errors [35].

A key component of this research was the use of a land-use regression (LUR) model of air pollution [34]. While the LUR model was independently validated and achieved decent overall results in its predicted estimates, the very nature of our study design ensures some degree of exposure misclassification to our study population. Our analysis was based on maternal place of residence at delivery, and therefore intra-urban commuting and potential inter-urban relocation within the pregnancy period was not accounted for which could affect the results. Time-activity patterns show that pregnant women spend more time at home in the later stages of pregnancy, but mobility patterns may differ by age, parity and SES [63,64]. Another limitation regarding the $PM_{2.5}$ exposure assessment is that the LUR model is cross-sectional based on 2006 air quality monitoring data, while the study period

of our perinatal dataset spans 6 years (2001 to 2006). We therefore assume all pregnancies were exposed to the same levels of $PM_{2.5}$ for their entire pregnancy, regardless of their year of birth, based on their residential DA. While this method prevents the assessment of exposure windows by trimester, spatiotemporal studies of $PM_{2.5}$ have shown little to no difference between trimester-specific and entire pregnancy effects on birth weight [3,46,48]. Finally, the mean $PM_{2.5}$ concentrations may be underestimated by the LUR model with less variability and missing several high $PM_{2.5}$ outlier locations in BC compared to compiled monitored data [26]. This could potentially result in an underestimation of our observed association of reduced birth weight with increasing $PM_{2.5}$ levels.

We were unable to control for maternal-level SES, and therefore the neighbourhood-level effect estimates and interactions could reflect individual-level differences. For example, the protective effect of older maternal age buffering the $PM_{2.5}$ effect on birth weight could be due to individual-level SES factors not accounted for in our models such as diet, income or stress. However, studies have found that adjustment for individual-level measures of SES did not significantly change the area-level associations [20,65]. Maternal education is a variable provided in the BC Perinatal Data Registry, but was only available for 10% of our population. However, the adjustment for socially-patterned behavioural risk factors such as maternal smoking, suspected drug or alcohol use and low number of prenatal care visits will control for some individual-level SES differences [66].

5.0 Conclusions

This study supports the growing literature of an effect of $PM_{2.5}$ on birth weight and its modification by both maternal and neighbourhood-level factors. Most notably, it shows that lower SES neighbourhoods may be more negatively affected by higher levels of $PM_{2.5}$. We observed both positive and negative interactions between maternal factors and $PM_{2.5}$ that require further scrutiny but may reflect a $PM_{2.5}$-oxidiative stress pathway expressed via either protective pre-conditioning or harmful overload. Targeted municipal-level interventions to reduce $PM_{2.5}$ and improved neighbourhood SES may help improve birth outcomes at the population-level.

6.0 Endnote for Chapter 4

Figure 16 and Table 8 below show the results from a model that was subsequently run after the initial manuscript for Chapter 4 was accepted for publication. This model (Model 5) does not substantially alter any of the results, interpretation, or conclusions from the previous models; however, it does provide a more nuanced understanding of the

observed relationships between $PM_{2.5}$, rural residence and SES on continuous birth weight. In Figure 16, the middle pane (Mean SES) corresponds to Figure 15c in the main text showing the more pronounced decline in birth weight for rural births with increasing levels of $PM_{2.5}$. By adding an interaction term between rural and SES, the stark contrast of the SES effect on urban and rural births becomes clear. The red line representing rural births remains fairly static, indicating that within rural areas SES has a limited role on birth weight, an observation that has been noted in other studies [67,68]. Conversely, the blue line representing urban births shows a dramatic increase in birth weight with increasing SES while its slope which signifies the $PM_{2.5}$ effect becomes slightly less steep demonstrating the protective role of improved SES on the negative effects of $PM_{2.5}$ on birth weight. Compared to Model 3 and 4, Model 5 shows to have a slightly better AIC score, as well as explaining slightly more of the DA-level variance in the random intercept.

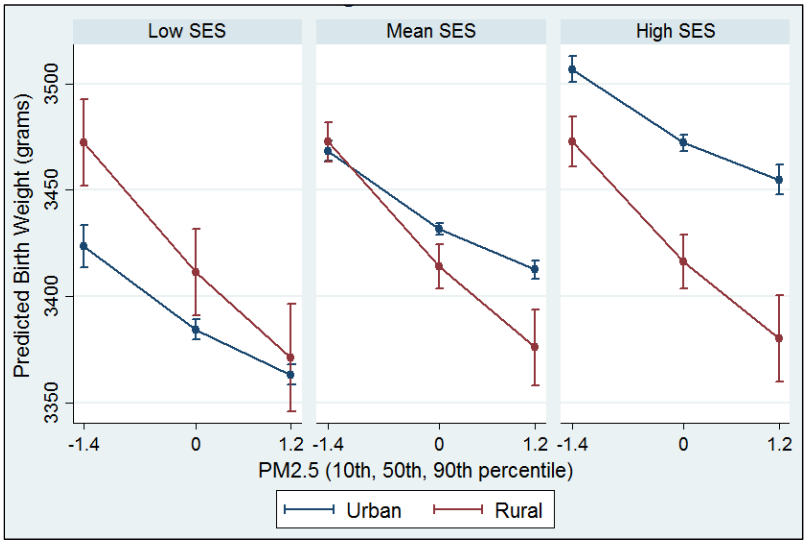

Figure 16: Results from Model-5 including a SES*Rural interaction

Table 8: Adjusted individual and DA-level fixed effects on continuous and term birth weight and their modification by $PM_{2.5}$ (Model-5)

Variables	Main Effect β (95%CI)	Modification by PM2.5 β (95%CI)
$PM_{2.5}$[a]	-21.0 (-23.7 – -18.2)	4.0 (2.2 – 5.7)
Cigarettes/day[a]	-21.9 (-23.6 – -20.1)	2.7 (2.1 – 3.3)
Drug/Alcohol flag	-80.5 (-92.9 – -68.2)	15.3 (4.4 – 26.2)
Maternal age	-4.3 (-6.3 – -2.3)	5.5 (3.7 – 7.3)
Gestational diabetes	70.3 (62.7 – 77.9)	-33.7 (-41.8 – -25.7)
SESi	33.7 (31.1 – 36.2)	1.3 (-1.4 – 3.9)
Immigrant density	-30.4 (-33.1 – -27.8)	3.7 (0.8 – 6.7)
Rural address	-17.7 (-28.3 – -7.1)	-15.7 (-23.7 – -7.6)
Rural*SESi	-31.8 (-42.1 – -21.4)	--
Random Effects & Model Diagnostics		
Variance Components		
L1 residual (sd)	435.2	
L2 intercept (sd)	36.4	
L2 slope (sd)	27.4	
Intercept	3521.22	
AIC	478665	
L1-PCV (%)	39.7	
L2-PCV (%)	78.7	
ICC/VPC #	0.007	

[a] Modeled as a quadratic, Cigarettes/day: 0.7(0.6 – 0.8); Model adjusted for gestational age, nulliparous, diabetes mellitus, gestational hypertension, prenatal care visits, season of birth, DA-level education, on-reserve birth.

7.0 References

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Chapter 5: Air pollution, neighbourhood and maternal-level factors modify the effect of smoking on birth weight: a multilevel analysis in British Columbia, Canada

Erickson A.C., Ostry A., Chan L.H.M., Arbour L. Air pollution, neighbourhood and maternal-level factors modify the effect of smoking on birth weight: a multilevel analysis in British Columbia, Canada. *BMC Public Health.* Accepted, in press.

Abstract

Background: Maternal smoking during pregnancy negatively impacts fetal growth, but the effect is not homogenous across the population. We sought to determine how the relationship between cigarette use and fetal growth is modified by the social and physical environment.

Methods: Birth records with covariates were obtained from the BC Perinatal Database Registry (N=232,291). Maternal smoking status was self-reported as the number of cigarettes smoked per day usually at the first prenatal care visit. Census dissemination areas (DAs) were used as neighbourhood-level units and linked to individual births using residential postal codes to assign exposure to particulate air pollution ($PM_{2.5}$) and neighbourhood-level attributes such as socioeconomic status (SES), proportion of post-secondary education, immigrant density and living in a rural place. Random coefficient models were used with cigarettes/day modeled with a random slope to estimate its between-DA variability and test cross-level interactions with the neighbourhood-level variables on continuous birth weight.

Results: A significant negative and non-linear association was found between maternal smoking and birth weight. There was significant between-DA intercept variability in birth weight as well as between-DA slope variability of maternal smoking on birth weight of which 68% and 30% respectively was explained with the inclusion of DA-level variables and their cross-level interactions. High DA-level SES had a strong positive association with birth weight but the effect was moderated with increased cigarettes/day. Conversely, heavy smokers showed the largest increases in birth weight with rising neighbourhood education levels. Increased levels of $PM_{2.5}$ and immigrant density were negatively associated with birth weight, but showed positive interactions with increased levels of smoking. Older maternal age and suspected drug or alcohol use both had negative interactions with increased levels of maternal smoking.

Conclusion: Maternal smoking had a negative and non-linear dose-response association with birth weight which was highly variable between neighbourhoods and evidence of effect modification with neighbourhood-level factors. These results suggest that focusing exclusively on individual behaviours may have limited success in improving outcomes without addressing the contextual influences at the neighbourhood-level. Further studies are needed to corroborate our findings and to understand how neighbourhood-level attributes interact with smoking to affect birth outcomes.

1.0 Background

Smoking during pregnancy is a modifiable risk factor associated with adverse birth outcomes and may impart long-term health consequences [1–3]. This relationship however is confounded by the presence of many other risk factors, including maternal age, education, alcohol or drug use [4–6]. Furthermore, it's been shown that these individual-level risk factors have a dose-response association with the level of smoking, with a distinction between heavy smokers (greater than 10 cigarettes per day) and moderate or light smokers [4]. For example, while the prevalence of smoking during pregnancy decreases with increasing maternal age, the level of smoking is heavier among the older mothers who do smoke. The effect of smoking on birth weight has been shown to be modified by maternal age and other behavioural risk factors [7,8]. Similarly, neighbourhood-level factors might directly or indirectly modify the effect of smoking on birth weight such as neighbourhood deprivation or levels of particulate air pollution [9–11].

Exposure to the fine fraction of particulate matter ($PM_{2.5}$, particles with aerodynamic diameter ≤ 2.5 μm) has shown to be a consistent risk factor associated with reduced birth weight [12]. The complex mixture of $PM_{2.5}$ includes elemental and organic carbon compounds, metals and gases that stem predominantly from vehicle exhaust, residential heating and industrial emissions [13].The mechanisms by which $PM_{2.5}$ and its constituents adversely affect the reproductive system are not fully understood; however, evidence supports the potential for a shared mode of developmental toxicity with tobacco smoke exposure [14–16]. With similar chemical components, both $PM_{2.5}$ and tobacco smoke penetrate deep into pulmonary alveolar tissues and translocate to extrapulmonary tissues causing systemic cardiovascular and immunological alterations, including platelet activation, coagulation, endothelial dysfunction, DNA damage and mutagenesis [13,16,17].

Low SES remains one of the most robust predictors of adverse pregnancy outcomes such as fetal growth restriction despite universal health care programs in Canada and

Europe [9,18,19]. The society-level determinants such as poverty, poor education, income inequality and social discrimination and marginalization act indirectly on the placenta and fetus through the promotion of 'downstream' or mediating exposures, stresses and behaviours [20,21]. In studies of cardiovascular disease, neighbourhood-level factors were associated with increased levels of smoking and other risk factors such as obesity, lack of exercise, lower health knowledge and lower positive behaviour changes [11,22]. These epidemiological observations have been shown with the use of multilevel statistical models capable of separating the individual-level effects from the context of their social and physical environments [23]. The use of multilevel models in perinatal epidemiology has uncovered neighbourhood-level factors that interact with maternal-level risk factors to either buffer or mediate adverse birth outcomes [21,24].

We present a multilevel cross-sectional analysis of birth registry data in British Columbia, Canada (population 4.6 million) to investigate neighbourhood-level differences in the effect of cigarette smoking during pregnancy on birth weight and to quantify the degree to which individual and neighbourhood-level variables explain any observed differences. Specifically, we sought to determine whether exposure to $PM_{2.5}$ and living in low SES neighbourhoods explain between-neighbourhood differences in the effect of maternal smoking on birth weight. We also examine whether these neighbourhood-level factors modify the direct effect of maternal smoking on birth weight. Birth weight is among the most important factors affecting neonatal mortality and is a significant determinant of post-neonatal infant mortality and childhood morbidity [25]. Understanding the underlying individual and interactive effects of exposures on birth weight is crucial for effective community planning and strategic interventions to improving reproductive health outcomes.

2.0 Data and Methods

This was a population-based cross-sectional study of singleton births in British Columbia from 2001 to 2006 (N=237,470). Data from the BC Perinatal Database Registry were provided by Perinatal Services BC (PSBC), and included information on individual-level maternal-infant health status and outcomes, reproductive history, socio-demographics, risk factors, and residential postal codes. The Registry accounts for 99% of births and stillbirths in BC of at least 20 weeks gestation or at least 500 grams birth weight. Research data access is provided by a Partnership Accord /Memorandum of Agreement between all BC Health Authorities and PSBC through the *Freedom of Information and Privacy*

Protection Act [26]. Research ethics board approval was granted by the University of Victoria (protocol #11-043).

The outcome variable was continuous birth weight of singleton births. Included were all births (stillbirth and live) for gestational ages of 20 to 42 weeks. Excluded birth records included: out-of-province and invalid postal codes (n=1,096), non-viable births prior to 20 weeks gestation and less than 500 grams (n=15), and the list-wise deletion of births missing important data including: cigarettes smoked per day (cigarettes/day, n=2,510), $PM_{2.5}$ (n=1,512), birth weight (n=46). Table 9 provides the full list of covariates used along with their summary statistics. All continuous independent variables, except cigarettes/day, were grand-mean centred and standardized to ease interpretation and aid model convergence. Thus, a value of zero represents the transformed variable's mean and reference value and has a standard deviation equal to one. The variable cigarettes/day was kept un-transformed since the value zero (i.e. non-smokers) was the desired reference level. Smoking levels were capped at 20 cigarettes/day with higher values assigned a value of 20 to stabilize the distribution tail (n = 245, min.21 max.80). Two variables indicating the use of alcohol or drug use (prescription, non-prescription, illicit) as a risk factor in the pregnancy identified by a physician were combined into a single dichotomous variable.

Birth records were geocoded based on the latitude-longitude coordinate of the mother's residential postal code at the time of delivery using *GeoRef* by DMTI [27]. Birth records were then linked to their corresponding census dissemination area (DA) by performing a point-in-polygon spatial join procedure in *ArcGIS 10.2* [28]. DAs represent the smallest geographical unit for which census data are available with a spatial coverage ranging between 200–800 people depending on the level of urban development. While DAs do not necessarily represent existing neighbourhood communities [29], they can act as proxies for a general catchment area of personal home-life activities [21,30]. Birth records were identified as being either rural or urban using the Statistics Canada Metropolitan Influence Zone (MIZ) codes which are based on commuting flows of small towns into larger cities and metropolitan areas [31].

$PM_{2.5}$ exposure was estimated using a national land-use regression (LUR) model developed to estimate $PM_{2.5}$ at the census street block-face level [32]. The model used a number of predictors including satellite measures, proximity to major roads and industry to account for 46% of the variability in measured annual $PM_{2.5}$ concentrations. Individual birth records were related to the block-face point estimates using a *nearest-point* procedure in

ArcGIS10.2. Street block-face point estimates were related to individual birth records using a *nearest-point* procedure in *ArcGIS10.2* and then aggregated to their DA-level mean to represent an area-level air pollution variable on individual births.

Three related but independent datasets all based on the 2006 Statistics Canada national census were used to represent the DA-level SES and demographic data. The first was a Canadian SES index (SESi) developed by Chan et al which provides a measure of overall socioeconomic neighbourhood well-being [33]. The second was the proportion of population over 15 with any post-secondary education, including college, trades, or university representing higher DA-level education attainment levels. The third was the proportion of continental Asian immigrants by DA. It's been shown in BC and elsewhere that healthy babies from Asian and South Asian backgrounds are constitutionally smaller compared to Caucasian babies [34,35]. Asian and South Asian ethnicities are well-represented throughout BC but particularly in concentrated pockets throughout the major urban center of Metro Vancouver where levels of $PM_{2.5}$ are also high and could therefore confound any $PM_{2.5}$ effect. Furthermore, concentrated ethnic communities may impart buffering mechanisms through enhanced social interactions and support networks [21,24]. A sequential regression technique was used to remove the collinearity between sets of DA-level variables [36]. Here, immigrant density was regressed against SESi and $PM_{2.5}$ with the saved residuals representing the uncorrelated and independent contribution of immigrant density on birth weight freed from its collinearity with SESi and $PM_{2.5}$ ($r = -0.62$ and 0.53 respectively). This method was repeated for SESi and education ($r = 0.26$) creating a residual immigrant density and residual education variable. The education and immigrant data were obtained by access to ABACUS via the Data Liberation Initiative [37].

Imputation for missing SES, education and immigrant density values was performed in order to avoid data loss of rural DAs with low population counts. Taking advantage of the nested hierarchical structure of the administrative census and health boundaries, the mean SESi value for a larger encompassing census subdivision (CSD) or local health area (LHA) was imputed for a nested DA with a missing value. There were 1,441 values imputed in 52 DAs for SESi (0.6% of final N, 0.8% of DAs), and 3,170 values imputed in 108 DAs for both education and immigrant density (1.4% of final N, 1.7% of DAs). Sensitivity analyses were performed using only the non-imputed data.

Hierarchical (multilevel) linear regression models were used to test our research questions, thereby accounting for the clustering, or non-independence, of individuals (level-

1) belonging to a given DA neighbourhood (level-2). The multilevel model allows the intercept and slope to act as random parameters having between-area (DA) variability from an overall (BC-wide) mean intercept and slope. Therefore each DA has its own intercept and slope in which their variability from the overall mean intercept and slope can be investigated with the addition of individual (level-1) and DA-level (level-2) variables and their interactions [38]. We followed a bottom-up approach to model building to quantify the explained proportional change in variance (PCV) with the addition of sets of variables, the multilevel model equivalent to an R^2 [23]. We started with the empty (Null) random intercept model without any independent variables in which birth weight is only a function of the mother's residential DA. The presence of significant random intercept variance indicates there are unexplained differences between neighbourhood means of birth weight. The proportion of the total variance in birth weight that arises due to neighbourhood differences can be quantified by computing the intra-class correlation (ICC) which represents the degree of clustering of individual birth weight within neighbourhoods [23].

The Null model was followed by Model that included the individual-level covariates as well as the addition of a random slope for the continuous variable of maternal smoking (cigarettes/day, self-reported at the first prenatal visit). By allowing cigarettes/day to be random, the mean within-DA effect of maternal smoking is allowed to differ between DAs. The presence of a significant random slope indicates that its effect on birth weight is not constant (or equal) for all DAs; that is, there are important unexplained differences between the within-DA group effects of maternal smoking on birth weight. Subsequent models included the DA-level variables along with cross-level interactions to assess their fixed effects on birth weight but to also determine if their inclusion addressed any unexplained slope variance. Several models were tested using the Akaike Information Criterion (AIC) to evaluate model performance. We report the results of three models to compare the degree of change between the level-1 and level-2 homogeneous (non-interaction) models and a model with effect-measure variation. Statistical analyses were conducted in *Stata 13IC* [39].

3.0 Results

After exclusions, the final dataset included 232,291 singleton (live and stillborn) births located in 6,338 neighbourhood DAs (min. = 1, max. = 782, avg. = 37). Table 9 summarizes the untransformed individual and neighbourhood covariates (non-centered, non-standardized). The prevalence of maternal smoking in this population was 10.3% (n = 23,836) with an average of 7.5 cigarettes/day among smokers. Table 10 reports the

adjusted coefficients for the individual and DA-level covariate fixed effects on continuous birth weight (Model 1 and 2). Model 1 was a level-1 model that included only the maternal-level covariates. The relationship between birth weight and cigarettes/day was found to be non-linear and was best modeled using a quadratic term indicating a subdued dose-response with increasing exposure (Figure 17). Model 2 added the DA-level variables. Their fixed effects show that DAs with higher SES and higher proportion of post-secondary education were significantly associated with higher birth weights; whereas DAs with increased levels of $PM_{2.5}$, higher Asian immigrant density and rural DAs were all significantly associated with lower birth weights. Season of birth (fall or winter) was also significantly association with reduced birth weight. The results in Table 10 represent the fixed effects from homogeneous models (i.e. those without any modeled heterogeneity of the effect measure for maternal smoking).

Table 9: Descriptive statistics# for individual (Level-1) and DA (Level-2) covariates on term birth weight

Variable	Mean (sd)	Min-Max
Level-1 (individual)		
Maternal age	29.8 (5.60)	11 – 55
Nulliparous	0.45 (0.50)	0 – 1
Drug/Alcohol flag	0.02 (0.15)	0 – 1
Cigarettes/day	0.79 (2.91)	0 – 20
Fall/Winter season	0.48 (0.50)	0 – 1
Level-2 (DA) Variables		
SESi	-0.08 (0.58)	-2.22 – 1.18
Education	0.50 (0.12)	0 – 0.95
Immigrant density	0.16 (0.19)	0 – 0.86
$PM_{2.5}$	7.30 (0.86)	4.41 – 10.23
Rural address	0.11 (0.32)	0 – 1

values shown are unstandardized, non-centered; Nulliparous: patient has never delivered a baby of at least 500 grams birth weight or at least 20 weeks gestation in a previous pregnancy; Drug or Alcohol Flag: physician indicated use of drugs (prescription, non-prescription, illicit) or alcohol as risk factor in pregnancy; Cigarettes/day: number of cigarettes smoked daily at 1st prenatal visit (self-reported); Fall/Winter Season: month or birth between September to February; SESi: socioeconomic status index; Education: proportion of population over 15 with any post-secondary education (trade, college, university); Immigrant Density: proportion of the population identified as immigrant status from continental Asia; $PM_{2.5}$: Particulate Matter less than 2.5 microns; Rural: those having a rural residential address.

Table 10: Adjusted fixed effects for level-1 and level-2 covariates on continuous term birth weight

Variables	Model 1 β (95%CI)	Model 2 β (95%CI)
Maternal age	-16.9 (-19.3 – -14.4)	-14.9 (-17.4 – -12.4)
Nulliparous	-107.7 (-112.5 – -103.0)	-105.5 (-110.3 – -100.7)
Drug/Alcohol flag	-171.6 (-186.9 – -156.3)	-172.2 (-187.5 – -157.0)
Cigarettes/day	-23.5 (-25.8 – -21.2)	-26.2 (-28.5 – -23.9)
cigarettes/day[a]	0.66 (0.51 – 0.80)	0.75 (0.61 – 0.90)
Fall/Winter season	-9.6 (-14.1 – -5.0)	-8.8 (-13.3 – -4.3)
SESi	--	42.7 (39.8 – 45.6)
Education	--	6.3 (3.5 – 9.1)
Immigrant density	--	-35.8 (-38.5 – -33.2)
Rural address	--	-18.8 (-28.4 – -9.2)
$PM_{2.5}$	--	-25.0 (-28.2 – -21.8)
$PM_{2.5}$ [a]		3.3 (1.5 – 5.2)

See Table 9 caption for variable definitions; [a] Modeled as a quadratic.

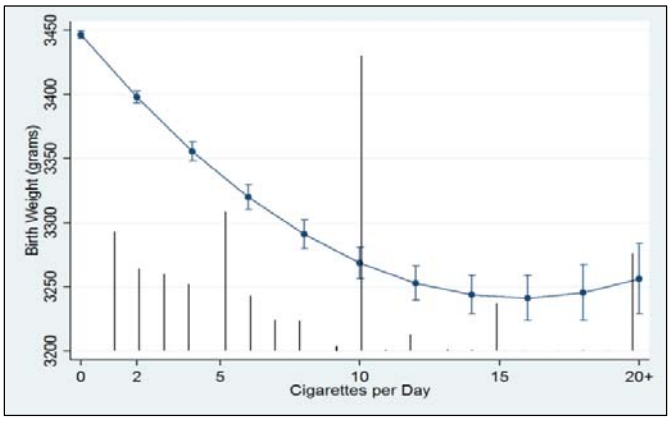

Figure 17: Adjusted Predicted Effects of Maternal Smoking on Birth Weight
Predicted effects of maternal smoking (cigarettes/day) on birth weight with 95% CIs are conditional on model covariates included in Model 3. Black vertical lines represent the frequency distribution of cigarettes/day (non-smokers, 0 cigarettes/day, have been omitted for display purposes).

Model 3 tested interactions with cigarettes/day including cross-level (level-1 by level2) and level-1 by level-1 interactions to explain the between-DA random intercept and random slope variability. The model results are presented in Table 11 including the main effects as well as the interaction effects with cigarettes/day. The degree of heterogeneity across levels of maternal smoking modified by the DA-level contextual factors is graphically presented in Figure 18. The five graphs show the predicted conditional fixed effects of SESi, education, $PM_{2.5}$, Asian immigrant density and rural residence on birth weight and their interactions with specified levels of maternal smoking (Figure 18A, 18B, 18C, 18D, and 18E respectively). For example, Table 11 and Figure 18A show that higher SES has a significant positive association with birth weight but is less pronounced with increased levels of maternal smoking whereby very heavy smokers (≥ 20 cigarettes/day) do not incur any

benefit of higher SES. Conversely, very heavy smokers showed the greatest gains in birth weight in DAs with higher proportions of post-secondary educated people (Figure 18B). Recall that the higher education variable was an uncorrelated residual variable independent of SESi, and therefore these observed associations are in addition to the education-related effect captured by SESi.

Table 11: Adjusted individual and DA-level fixed effects on continuous birth weight and their modification by maternal smoking (Model 3)

Variables	Main Effect β (95%CI)	Modification by Cigarettes/day β (95%CI)	Corresponding Figure
Cigarettes/day[a]	-25.7 (-28.1 – -23.3)	0.83 (0.68 – 0.98)	1
SESi	43.8 (40.9 – 46.8)	-2.7 (-3.7 – -1.6)	18A
Education	5.2 (2.3 – 8.1	1.3 (0.3 – 2.3)	18B
$PM_{2.5}$	-26.3 (-29.6 – -23.0)	1.8 (0.9 – 2.7)	18C
$PM_{2.5}$[a]	3.4 (1.5 – 5.3)		
Immigrant density	-36.5 (-39.2 – -33.7)	2.6 (1.5 – 3.7)	18D
Rural address	-15.0 (-25.1 – -5.0)	-2.9 (-5.6 – -0.2)	18E
Maternal age	-12.1 (-14.8 – -9.5)	-2.9 (-3.6 – -2.1)	19A
Drug/Alcohol flag	-161.2 (-180.4 – -142.1)	-3.7 (-6.3 – -1.2)	19B

See Table 9 caption for variable definitions; [a] Modeled as a quadratic; Model 3 covariates not listed: nulliparous and season of birth.

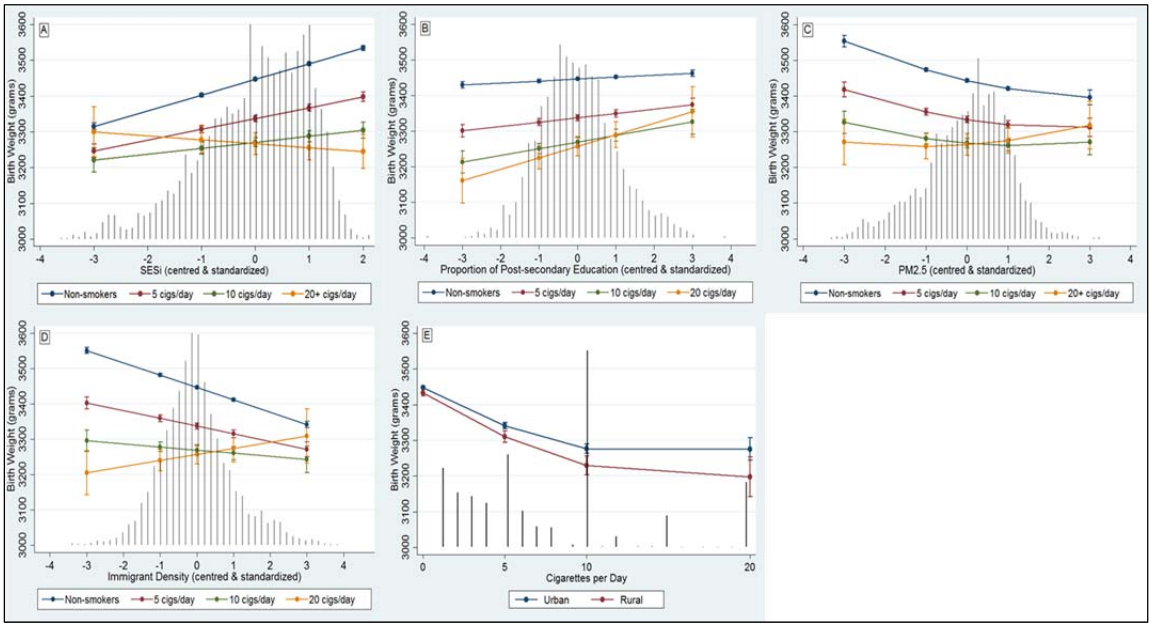

Figure 18: Adjusted Predicted Effects of Maternal Smoking on Birth Weight across DA-level Factors.

A) Socioeconomic Status Index B) Proportion of Population with Post-secondary Education C) $PM_{2.5}$ D) Asian Immigrant Density E) Rural Residence. Predicted effects on birth weight with 95% CIs are conditional on model covariates included in Model 3. Black vertical lines represent the frequency distribution of the variable on the x-axis (except Figure 18E which shows the frequency distribution of cigarettes/day).

Increasing $PM_{2.5}$ levels had a significant non-linear association with reduced birth weight; however, it showed a positive interaction with maternal smoking such that the effect of increased smoking on birth weight was attenuated in DAs with higher levels of $PM_{2.5}$ (Figure 18C). Similarly, higher Asian immigrant density was significantly associated with lower birth weights but had a positive interaction with increased cigarette use demonstrating a protective effect of higher immigrant density DAs (Figure 18D). Rural DAs had a significant negative interaction with maternal smoking indicating a further reduction in birth weight with increased cigarette use among rural residents (Figure 18E).

Two level-1 interactions with maternal smoking were significant, maternal age and suspected drug or alcohol use. The predicted conditional marginal effects of these two interactions are show in Figure 19A and 19B respectively indicating that the reduction of birth weight among heavier smokers is exasperated by older maternal age and those suspected of drug or alcohol use. A variable for neighbourhood-level smoking (DA-average cigarettes/day) was created and tested in models along with a cross-level interaction with maternal-level cigarettes/day but neither parameters were significant nor explained any additional variability.

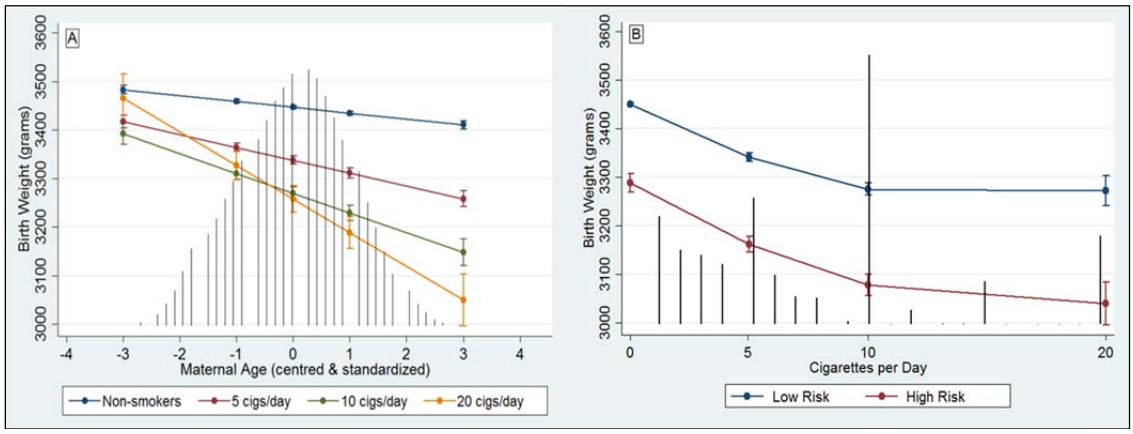

Figure 19: Adjusted Predicted Effects of Maternal Smoking on Birth Weight across Maternal-level Factors.

A) Maternal age B) Suspected Drug or Alcohol Use. Predicted effects on birth weight with 95% CIs are conditional on model covariates included in Model 3. Black vertical lines represent the frequency distribution of the variable on the x-axis (except Figure 19B which shows the frequency distribution of cigarettes/day).

The random effects, the explained proportional change in variance (PVC), and model diagnostics are presented in Table 12. The unadjusted ICC for the Null random intercept model was 0.019, indicating that 1.9% of the total residual differences in birth weight are attributable to DA-level contextual factors. However, the ICC increased to 2.2% for Model 1 with the inclusion of the level-1 covariates and random slope for cigarettes/day. This was

due to the reduction in the level-1 residual variance (560.5 to 554.7) relative to the increase in the level-2 random intercept variance (78.7 to 83.4). The (now adjusted) ICC_{adj} is conditional for the individual composition of the DAs, including the random slope for cigarettes/day held constant at 0 (i.e. non-smokers). The addition of DA-level variables in Model 2 removed a lot of the DA-level variance reducing the ICC_{adj} to 0.6%.

Table 12: Random Effects and Model Diagnostics

	Null Model	Model 1	Model 2	Model 3
L1 residual (sd)	560.5	554.7	555.0	554.9
L2 intercept (sd)	78.7	83.4	44.4	44.2
L2 slope (sd)	--	10.7	9.8	9.0
Intercept	3434.3	3505.9	3501.8	3500.9
AIC	602672	598513	596639	596514
L1-PCV	Ref.	2.0%	2.0%	2.0%
L2-PCV	Ref.	-12.3%	68.2%	68.5%
ICC/VPC[#]	0.019	0.022	0.006	0.006
Int-slope corr.	--	-0.53	-0.28	-0.28

L1 residual (sd): Level-1 residual standard deviation; L2 intercept (sd): Level-2 random intercept standard deviation; L2 slope (sd): Level-2 random slope standard deviation; PCV: proportional change in variance; [#]VPC (variance partition coefficient) is equivalent to the ICC but conditional on the random-slope variable, thus values in table represent intercepts for non-smoking individuals; Int-slope corr: intercept-slope correlation.

The level-2 random intercept variance term (reported as standard deviations in Table 12) indicates that the mean birth weight for every DA has a degree of variability from the overall (BC-wide) mean birth weight. For the Null model, the overall birth weight intercept is 3,434.3 grams with a standard deviation of 78.7 giving an 8.6% difference in range between 95% of the DAs (3,434.3 ± (1.96 x 78.7) = 3,280.0 and 3588.6 grams). The quadratic form of the random slope for cigarettes/day in Model 1 prevents a similar calculation to be performed, but Figure 20 gives an indication of the large between-DA slope variability which shows the DA-specific slopes of maternal smoking on birth weight. The intercept-slope correlation listed in Table 12 indicates the presence of DA-level heterogeneity signifying that DAs with higher average birth weights from non-smoking mothers have a lower within-DA effect of smoking (i.e. higher average DA intercepts of birth weight tend to have lower average slopes for smoking) [23,38].

The level-1 and level-2 explained PCV (L1-PCV & L2-PCV) summarizes the relative degree of explained variance at the different levels between the different models (Table 12). Using the Null model as the reference, the Model 1 resulted in an L1-PCV of 2.0%, and the

L2-PCV in the random intercept was -12.3%. The negative L2-PVC is a result of the larger level-2 intercept variance relative to the Null model. The addition of the DA-level variables in Model 2 explained 68.2% of the DA-level variance compared to the Null model. Model 3 accounted for an additional 0.3% of the L2-PCV.

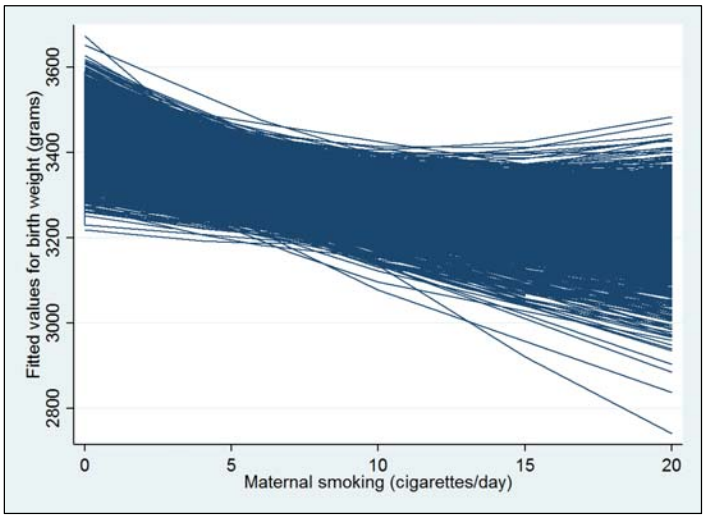

Figure 20: Neighbourhood-specific slopes of maternal smoking on birth weight
Empirical Bayes predictions of DA-specific regression lines for Model 1.

Sensitivity analyses using only the non-imputed DAs (N_1=229,067 in 6,230 DAs) showed very minor differences in magnitude of significant variables. Most of the DAs that were missing data were in rural areas with small population numbers, the likely reason why their data were suppressed from the census tables. While some parameters were slightly attenuated, many of the interaction terms increased in magnitude. The random intercept standard deviation was also slightly smaller than that of the same model using the full dataset while random-slope standard deviation showed no difference. In a second sensitivity analysis, we restricted the sample to only term births excluding stillbirths and congenital anomalies. As expected, there was a large reduction in the random slope variability (L2 slope (sd) = 5.7) and a small decrease in the random intercept variability (L2 intercept (sd) = 43.0) due to using only term births. Changes in the coefficients for the DA-level variables as well as their cross-level interactions with cigarettes/day were minor and within their 95% confidence intervals reported in Table 11. The exception was the main effect of education which was no longer significant (p=0.151), but its interaction with cigarettes/day remained significant (p=0.025). The maternal-level variables were attenuated but remained significant with the exception of the interaction between drug/alcohol flag and cigarettes/day which was no longer significant (p=0.106).

4.0 Discussion

This study employed multilevel random coefficient models to assess whether neighbourhood-level contextual factors can modify the effect of maternal smoking on birth weight. Our results show that the effect of maternal smoking on birth weight, self-reported as the number of cigarettes smoked per day, is modified by both individual-level and neighbourhood-level variables. However, the observed direction of the effect modification was not always as expected. Furthermore, through the use of random-slope models we show that the average effect of maternal smoking on birth weight can vary considerably between neighbourhoods which was only partially explained by the cross-level interactions. After adjusting for individual-level covariates and DA-level socio-economic, socio-demographic and air quality variables, there was a significant non-linear effect between cigarettes/day and birth weight in BC for singleton births from 2001 to 2006. This association was robust to the exclusion of stillbirths and congenital anomalies as well as the use of only term births demonstrating that selection bias does not likely affect the observed results.

The observed non-linear association between cigarettes/day and birth weight shown in Figure 17 suggests that the largest potential effects are seen at the low to middle range of smoking levels. England et al [40] found a very similar non-linear association of maternal smoking on term birth weight using self-reported cigarettes/day as well as using urine cotinine concentrations. Therefore, efforts to reduce the number of cigarettes smoked during pregnancy may have limited results for moderate and heavy smokers without substantial reductions or full cessation [41]. Interestingly, we found a similar curvilinear relationship with increasing levels of modeled $PM_{2.5}$ and birth weight (Figure 18C), a dose-response phenomenon observed in other exposure-disease contexts [42].

Beyond the non-linear association between cigarettes/day and birth weight, other factors were able to modify this relationship both positively and negatively. Our analysis confirm previously shown modification of the smoking-birth weight relationship by maternal risk factors [7,8]; however, to our knowledge this is the first study to show that neighbourhood-level factors are able to modify this relationship. We found a significant negative interaction between cigarettes/day and neighbourhood-level SESi that resulted in the attenuation of the beneficial role of rising neighbourhood-level SES on birth weight with increased levels of maternal smoking. The predicted effects presented in Figure 18A suggests is that maternal smoking may have little relevance in affecting birth weight in very

low SES neighbourhoods, but becomes more prominent as neighbourhood-level SES increases and perhaps other stressors negatively impacting birth weight are reduced. Hence interventions focusing exclusively on individual behaviours may have limited success without addressing the contextual influences at the neighbourhood-level [9,43–45].

Conversely, the small but significant positive interaction between higher proportions of neighbourhood-level post-secondary education and cigarettes/day found that heavy smokers may benefit the most by living in higher educated neighbourhoods (Figure 18B). This type of cross-level effect has been observed in other epidemiological scenarios where higher risk individuals have better outcomes than would be expected due to some beneficial capacity of the neighbourhood context [11,22]. The mechanisms by which neighbourhood-level factors affect individual health is indirectly exerted through individual-level processes, such as behaviours, adaptations and attitudes which may be transmitted between people [46,47]. Meng et al found that low education neighbourhoods exert an impact on low birth weight and preterm birth through unhealthy behaviours, psycho-social stress (i.e. sense of control) and SES-related support [21]. Therefore it could be that smoking cessation rates in pregnancy are higher in better educated neighbourhoods where healthier behaviours are more common [48,49]. Figure 18B suggests that living in higher educated neighbourhoods may encourage moderate and heavy smokers to reduce their smoking frequency to less than five cigarettes/day.

Neighbourhood social supports and transmission of behaviours could also explain the observed interactions with higher immigrant density and rural address, albeit in opposite directions. The positive interaction between higher immigrant density and maternal smoking (Figure 18D) may reflect the buffering effect of strong community cohesiveness and beneficial cultural practices [21,43,47]. Conversely, the observed negative interaction between rural address and cigarettes/day (Figure 18E) could be due to the transmission of negative behaviours being more common [50], and where less support for cessation may lead to smoking throughout pregnancy [51]. The dichotomized definition used to represent rural residential addresses may obscure mechanisms which can be modified by maternal factors such as education [52].

The buffering effect of $PM_{2.5}$ with increased levels of maternal smoking (Figure 18C) is curious but could provide evidence for a protective pre-conditioning stress that activates an adaptive response and increases biological resistance to cigarette-induced harms [53,54]. We found a similar positive interaction between suspected alcohol and drug use and $PM_{2.5}$

in a different analysis [55]. The suspicion of survival bias due to competing risks was partly mitigated by using a near full population sample that included stillbirths, congenital anomalies and preterm births, although we were not able to control for fetal loss prior to 20 weeks gestation. Other explanations require further scrutiny as evidence of the opposite (negative and synergistic) effect between smoking and air pollutants has been shown [10,16].

We have shown in an earlier paper that women who reported smoking 10 or more cigarettes/day at their first prenatal visit were significantly more likely to have other maternal risk factors, such as lower education, suspected drug or alcohol use, and fewer prenatal care visits [4]. Our current results compliment this previous study by showing that the cumulative impact of multiple risk factors can have more than an additive effect on birth weight reduction. The negative association between older maternal age and birth weight was markedly greater with increased levels of maternal smoking, particularly among the heaviest smoking group (Figure 19A). Similarly, those who reported higher levels of smoking who were also suspected of drug or alcohol use showed a pronounced effect compared to those who reported to not smoke (Figure 19B). These results corroborate the established literature showing similar synergistic interactions between both maternal alcohol use and smoking on lower birth weights [8,56], as well as between maternal smoking and older maternal age on birth weight [7,57].

While the application of multilevel models in perinatal epidemiology have become more common [58], most have been random intercept models with very few including a random-slope parameter. Permitting the slope for the maternal cigarettes/day exposure to be random provides information on how its effect on birth weight differs between neighbourhoods and enables the search for neighbourhood-level variables to help explain the between-neighbourhood variance [38]. For example, the random-slope standard deviation presented in Table 12 drops from 10.7 in Model 1 to 9.0 in the fully adjusted Model 3. This represents a 30% change in explained random-slope variance (10.7^2 – $9.0^2/10.7^2$). Furthermore, the addition of the level-2 variables explained 68.5% of the random intercept variance compared to the Null (empty) model. However in light of these findings, significant inter-DA variance remained for both the random intercept and slope.

This study used self-reports of smoking (cigarettes/day) recorded at the first prenatal visit; however, there were no data on exposure to environmental tobacco smoke or whether smoking reduction or cessation occurred during the pregnancy. The self-reporting bias of

cigarette consumption can lead to the attenuation of the true effect of smoking on birth weight [59], and may therefore alter observed interactions. Studies of smoking misclassification in the United States have estimated non-disclosure to be around 20% [60,61]. The demographic predictors of non-disclosure include former smokers and younger maternal age which could partially explain the observed interaction between maternal age and cigarettes/day [61]. Similarly, recall bias and perceived stigma may result in under-reporting of actual consumption habits. This could account for the observed curvilinear effect on birth weight if women smoking 10 cigarettes/day report only smoking 5 per day, although England et al observed a similar slope using urine-cotinine concentrations [40]. While relatively small, the list-wise deletion of observations with missing smoking data may exclude potentially at-risk pregnancies and could therefore alter coefficient estimates (n = 2,501, 1.1% of sample).

Another limitation includes potential measurement error and misclassification bias in the $PM_{2.5}$ exposure assessment which could affect its estimates. First, the LUR $PM_{2.5}$ concentrations may be underestimated with less variability compared to compiled monitoring data which could potentially underestimate its association with birth weight in certain areas [62]. Also the $PM_{2.5}$ LUR model is cross-sectional based on 2006 air quality monitoring data, and we therefore assume that the study population was exposed to the same levels of $PM_{2.5}$ across six year study period based on their residential DA. Finally, our analysis was based on maternal place of residence at delivery, and therefore intra-urban commuting and potential inter-urban relocation within the pregnancy period was not accounted for. Time-activity patterns show that pregnant women spend more time at home in the later stages of pregnancy, but mobility patterns may differ by age, parity and SES [63,64].

A main strength of this study is the quality of the perinatal registry data [65]. The near 100% ascertainment of birth records for the province of BC and quality control measures used in database management practices produces highly reliable data on maternal and newborn health outcomes, co-morbidities and exposures. However, the inability to control for individual-level SES, particularly maternal education, may influence the neighbourhood-level effect estimates and interactions. Maternal education is a variable provided in the PSBC Perinatal Registry, but was only available for 10% of our population cohort. The adjustment for socially-patterned behavioural risk factors such as maternal smoking and suspected drug or alcohol use will control for some individual-level SES

differences [4]. Notwithstanding, our results suggest that reported number of cigarettes smoked correlates with a substantial reduction in birth weight and is modified by socio-economic, demographic and environmental risk factors suggesting the information as provided will help identify those at highest risk.

5.0 Conclusions

The effect of maternal smoking on birth weight is not constant across geography, but rather is context specific given the social and physical environment. The use of random coefficient models revealed neighbourhood-level differences in how maternal smoking negatively impacted birth weight and demonstrated effect modification by neighbourhood and maternal-level factors. The inclusion of the DA-level SES, demographic and $PM_{2.5}$ variables explained 68.5% of the random intercept variability in DA-mean birth weight. However, the random slope variability was only partially explained by the cross-level interactions suggesting other contextual factors are involved in determining the magnitude of maternal smoking on birth weight. Further studies are needed to corroborate our findings and to understand how neighbourhood-level attributes interact with smoking to affect birth outcomes.

6.0 References

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Chapter 6: Association of Gestational Diabetes and Hypertension with increased fine particulate matter and neighbourhood-level socioeconomic factors: a multilevel analysis in British Columbia, Canada

Abstract

Background: Gestational diabetes (GDM) and gestational hypertension (GH) are independent risk factors of preterm birth and low birth weight, and have been associated with increased exposure to particulate matter ($PM_{2.5}$). The purpose of this research was to determine the relationship between modeled particulate matter ($PM_{2.5}$) exposure and gestational diabetes and hypertension and the potential modification by indicators of socioeconomic status (SES) and maternal BMI.

Methods: Birth records from 2001 to 2006 (N = 166,369 and 165,727 for GH and GDM respectively) were linked to modeled $PM_{2.5}$ data from a national land-use regression model along with neighbourhood-level SES and socio-demographic data using 6-digit residential postal codes. Logistic multilevel random intercept models were used to estimate the effects of $PM_{2.5}$, SES and other individual and neighbourhood-level covariates on GDM and GH.

Results: The incidence of GH and GDM was 2.4% and 6.8% respectively across the 6-year study period. $PM_{2.5}$ was significantly associated with an increased risk for both GH and GDM, (highest vs. lowest quintile, OR 95% CI = 1.69 (1.51 – 1.91), and 1.63 (1.50 – 1.78), respectively) after adjusting for individual and neighbourhood-level covariates. Higher neighbourhood-level SES as well as higher educational attainment were both associated with a lower risk of GH and GDM, while higher immigrant density and higher DA-mean BMI showed an increased risk. GDM showed considerable effect heterogeneity in urban areas where the interaction between $PM_{2.5}$ and SES greatly modified the risk of GDM. These associations were more pronounced among mothers with larger pre-pregnancy BMI.

Conclusion: This study supports the growing literature of the association of $PM_{2.5}$ on the risk of GH and GDM and provides new insights into the role of neighbourhood-level SES and demographic factors. The implications of a potential link between GH and GDM with $PM_{2.5}$ exposure are profound as this air pollutant is pervasive throughout the world, and therefore even modest mitigation in exposure will provide substantial public health benefits.

1.0 Background

Gestational diabetes mellitus (GDM) and gestational hypertension (GH) are two complex pregnancy conditions that affect between 3-6% and 3-9% of pregnancies respectively, with rates for both conditions increasing in Canada [1–4]. GH, defined here as excluding the more severe diagnosis of preeclampsia, and GDM are both associated with increased risk of maternal and fetal/infant morbidities and mortality [3–6]. Women who develop these conditions during pregnancy have an increased lifetime risk of developing type 2 diabetes, cardiovascular disease and obesity later in life [5,7]. Although they are independent conditions, they share several risk factors such as increased body mass index (BMI), family history, and older maternal age [6,8]. Recently, there is accumulating evidence supporting their association with exposure to air pollution [9–15].

Particulate air pollution less than 2.5 microns ($PM_{2.5}$) is a complex mixture of elemental and organic carbon compounds, metals and gases that stem predominantly from vehicle exhaust, residential heating and industrial emissions. $PM_{2.5}$, which includes ultrafine particles less than 0.1 microns, can penetrate deep into the pulmonary alveolar tissue where inflammatory mediators and possibly the particles themselves translocate into the bloodstream causing systemic cardiovascular, metabolic, and immunological alterations. These include systemic inflammation, platelet activation, coagulation, elevated leptin, reduced adiponectin, and endothelial dysfunction [16–22]. Increased oxidative stress and inflammation in both GDM and GH have been observed in previous studies [13,14,16,17]. While the epidemiological evidence linking $PM_{2.5}$ to acute and chronic hypertension and cardiovascular diseases is well established [21,23–26], the literature supporting the association between diabetes and $PM_{2.5}$ is more recent [16,18,27–29].

The impact of the social environment on indicators and biomarkers of cardiovascular and metabolic system diseases is well documented [30–34], and lower SES has been associated with higher prevalence of both GDM and GH [10,35]. The social environment can be conceptualized as a series of overlapping hierarchical structures within which individuals are nested in neighbourhoods and communities with their own set of attributes that can promote or antagonize health and healthy behaviours [36–41]. This mix of individual-level observations clustered within neighbourhoods with their own distinct attributes creates opportunities to quantify the degree of influence neighbourhood factors have on individual-level health outcomes as well as potential interactions between them [42,43].

We present a multilevel retrospective cohort analysis of the association between GDM and GH with $PM_{2.5}$ and SES in British Columbia, Canada. We use random intercept logistic regression models to explore the between-neighbourhood variability in the risk of GDM and GH and whether interactions with $PM_{2.5}$, neighbourhood-level SES indicators, and/or individual-level risk factors are able to explain any observed variability.

2.0 Data and Methods

This was a population-based retrospective cohort of singleton births in British Columbia from 2001 to 2006 (N=237,470). Data from the BC Perinatal Data Registry were provided by Perinatal Services British Columbia (PSBC) which included information on maternal-infant health status and outcomes, reproductive history, maternal risk factors, attributes, and residential postal codes. The Registry accounts for 99% of births and stillbirths in BC of at least 20 weeks gestation or at least 500 grams birth weight. Research data access is provided by a Partnership Accord / Memorandum of Agreement between all BC Health Authorities and PSBC through the *Freedom of Information and Privacy Protection Act* [44]. Research ethics board approval was granted by the University of Victoria (ethics protocol #: 11-043).

The two outcome variables were gestational hypertension (GH) and gestational diabetes mellitus (GDM). The diagnosis of GH (in isolation of proteinuria) is the indication that the mother had an antepartum blood pressure reading of greater than or equal to 140/90 on two consecutive readings during the current pregnancy. However, it is important to note that this variable is limited to the degree that it does not imply the hypertension was induced by the current pregnancy, and that the mother could have had chronic hypertension. The diagnosis of GDM is the indication that the mother developed carbohydrate intolerance during pregnancy, which has been controlled by diet or requires insulin to regulate blood glucose levels. A positive diagnosis for GDM requires a minimum of two abnormal readings (out of four) in the glucose tolerance test [44]. The hypothesized causal pathways for both outcomes are presented in Figure 21.

In order to avoid potential selection bias [45,46], we included all births (stillbirth and live) for all gestational ages (20-42 weeks). Excluded records included out-of-province and invalid postal codes (n=1,096), non-viable births prior to 20 weeks gestation *and* less than 500 grams (n=14), and missing $PM_{2.5}$ (n=1,510). Due to the substantial amount of missing maternal BMI values (n = 68,407; 29%), two sets of models were run using complete-case assessment and multiple imputation as a sensitivity analysis.

The spatial location of each birth record was geocoded based on the latitude-longitude coordinate of the mother's residential postal code at the time of delivery using *GeoRef* [47]. Birth records were related to their corresponding census dissemination area (DA) by performing a point-in-polygon spatial join procedure in *ArcGIS 10.2* [48]. DAs are the smallest geographical unit for which census data are available and represent neighbourhood blocks ranging between 200–800 people. While DAs do not necessarily represent existing neighbourhood communities [49], they can act as proxies for a general catchment area of personal home-life activities [50,51]. Birth records were identified as being either rural or urban using the Statistics Canada Metropolitan Influence Zone (MIZ) codes which are based on commuting flows of small towns into larger cities and metropolitan areas [52].

Exposure to $PM_{2.5}$ was estimated using a national land-use regression (LUR) model developed to estimate $PM_{2.5}$ at the census street block-face level [53]. The model used a number of predictors including satellite measures, proximity to major roads and industry to account for 46% of the variability in measured annual $PM_{2.5}$ concentrations. Unlike nitrogen dioxide (NO_2), $PM_{2.5}$ tends to have a more homogeneous intra-urban distribution between personal, indoor and ambient [54]. The LUR model estimates used for this study showed very little variability of $PM_{2.5}$ exposures between individuals within a given DA. We therefore aggregated the point-level estimates of $PM_{2.5}$ to their DA-level mean and related it to individual birth records as an area-level variable.

The DA-level SES and demographic data were represented by three related but independent datasets all based on the 2006 Statistics Canada national census. The first was a Canadian SES index (SESi) developed by Chan et al [55]. The second was an education variable representing the proportion of population over 15 with any post-secondary education, including college, trades, or university. The third was the proportion of continental Asian immigrants including the Middle East and South Asia. It's been shown that these ethnic populations tend to have higher rates of GDM and/or GH compared to their Caucasian counterparts [35,56,57]. Asian and South Asian ethnicities are well-represented throughout BC, but particularly in concentrated pockets throughout the major urban center of Metro Vancouver where levels of $PM_{2.5}$ are also high. Collinearity between the DA-level variables was eliminated using a sequential regression technique to create uncorrelated and independent variables for education and immigrant density [58]. The education and immigrant data were obtained by access to ABACUS via the Data Liberation Initiative [59].

All continuous variables were standardized and centered to ease interpretation and aid model convergence.

In order to avoid data loss from rural DAs, imputation for missing SES, education, and immigrant density values was performed. Taking advantage of the nested hierarchical structure of the administrative census and health boundaries, the mean value for a larger encompassing census subdivision (CSD) or local health area (LHA) was imputed for a nested DA with a missing value. There were 1,441 values imputed in 52 DAs for SESi (0.6% of final N, 0.8% of DAs), and 3,170 values imputed in 108 DAs for both education and immigrant density (1.4% of final N, 1.7% of DAs). Sensitivity analyses were performed using only the non-missing data.

Multilevel (random intercept) logistic regression was used to test our research questions. This allowed us to account for and measure the degree of clustering of individuals (level-1) belonging to a given DA neighbourhood (level-2), as well as quantify the between-area variability in disease risk before and after adjustment for level-1 and level-2 risk factors. This example of a generalized linear mixed model allows the intercept to act as a random parameter with each DA having its own intercept that varies from the overall (BC-wide) intercept. Any explained variability can then be investigated and measured with the addition of level-1 and level-2 variables and their interactions [60]. We followed a bottom-up approach to model building to quantify the explained proportional change in variance (PCV), the multilevel model equivalent to an R^2 [43]. We started with an empty (null) random intercept model without any independent variables in which the probability of GH or GDM is only a function of the mother's residential DA. The presence of significant random intercept variance indicates there are unexplained differences between neighbourhoods in the risk of GH and GDM. We calculate the median odds ratio (MOR) to translate the area-level variance to the odds ratio scale which permits the direct comparison of its magnitude to that of the level-1 and level-2 factors [61,62]. The MOR depends directly on the area-level variance and is defined as the median odds ratio between any two areas picked at random with differing risk (i.e. what is the median increase in risk for an individual moving to an area with a higher risk).

Subsequent models included the individual and DA-level variables along with cross-level and within-level interactions in order to assess their fixed effects on the outcomes. Specifically, we were interested in two effect interaction models. First, does the association of $PM_{2.5}$ on GDM and GH differ by SES status; and second, is there effect heterogeneity by

BMI status. Models were then compared to determine how much the inclusion of certain sets of variables addressed any unexplained intercept variance. Models were tested using the Akaike Information Criterion (AIC) to evaluate model performance. All statistical analyses were conducted in *Stata 13IC* [63].

We conducted several sensitivity analyses to test the robustness of the results. First, to determine if the missing BMI data biased model estimates, multiple imputation was performed [64]. We were also interested if maternal level education would attenuate the DA-level education and SES associations. Imputed Chained Equations (ICE) were used to impute 68,151 missing BMI values and 205,889 missing maternal education values. All covariates, exposure and outcome variables were included in the imputation process, and twenty sets of missing values were imputed after an initial burn-in of 10 iterations [65]. We used logistic regression with robust standard errors to estimate the models within the multiple imputation framework to account for clustering of individuals within DAs.

Second, we used abnormal glucose factor (AGF) as an indicator of pre-GDM and test its association with $PM_{2.5}$ and SES variables. AGF indicates the possible presence of gestational diabetes in pregnancy, without confirmation of diagnosis (e.g. the mother may have one abnormal glucose tolerance test, carbohydrate intolerance, but a diagnosis of diabetes has not been made) [44]. Lastly, we used tests for spatial autocorrelation (local Moran's *I* statistic) to check for residual spatial autocorrelation in the residuals that would indicate the existence of unobserved spatial processes causing DAs to cluster and a sign of possible model misspecification [66]. We then ran spatial lag regression models to quantify the magnitude of any remaining spatial dependence using the level-1 adjusted random intercept residuals as the DA-level dependent variable. Due to the presence of islands (DAs with no neighbours), we used a nearest neighbour of 7 (KNN = 7) spatial weight matrix as it was the most frequent neighbour amount and produced the highest Moran's *I* values when testing model random effects (compared to KNN of 4, 5, 6, 8, 10, 15). Prediction of the DA-level random intercept error used an Empirical Bayes method available as a post-estimation command in *Stata 13IC* [67].

3.0 Results

Due to differences in the exclusion criteria, the total number of births for GH and GDM differed. There were 166,369 and 165,727 singleton (live and stillborn) births for GH and GDM respectively located in 6,312 neighbourhood DAs (min. = 1, max. = 698/694, avg. = 26). Table 13 summarizes the untransformed individual and neighbourhood covariates

(non-centered, non-standardized). Older maternal age, larger BMI, and higher $PM_{2.5}$ were notably higher in both GH and GDM cases; whereas rural residence had a notable lower proportion of GH and GDM diagnoses. Table 14 reports the adjusted odds ratios (ORs) with 95% confidence intervals (95% CI) for GH and GDM in relation to the $PM_{2.5}$ quintiles as well as the DA-level variables. In addition to the random intercept (RI) model estimates, the results from the multiple imputed (MI) estimation are also reported. The results show a similar dose-response association between the risk of both GH and GDM with increasing $PM_{2.5}$ concentrations. Higher immigrant density also showed an increased risk for both GH and GDM, while higher SES and DA-level education showed protective associations. The multiple imputed model for GH (GH-MI-m1) showed a slight attenuation in the ORs for $PM_{2.5}$ and immigrant density, but remain significant. Conversely, the multiple imputed model for GDM (GDM-MI-m1) showed a slight increase in the ORs for $PM_{2.5}$ but are attenuated (shift toward one) for the other DA-level variables. The imputation and inclusion of maternal-level education may have had an attenuating effect on the DA-level SES and higher education in the model for GDM more so than for GH, but both remain significant predictors in their respective models. The results are graphically presented in Figure 22.

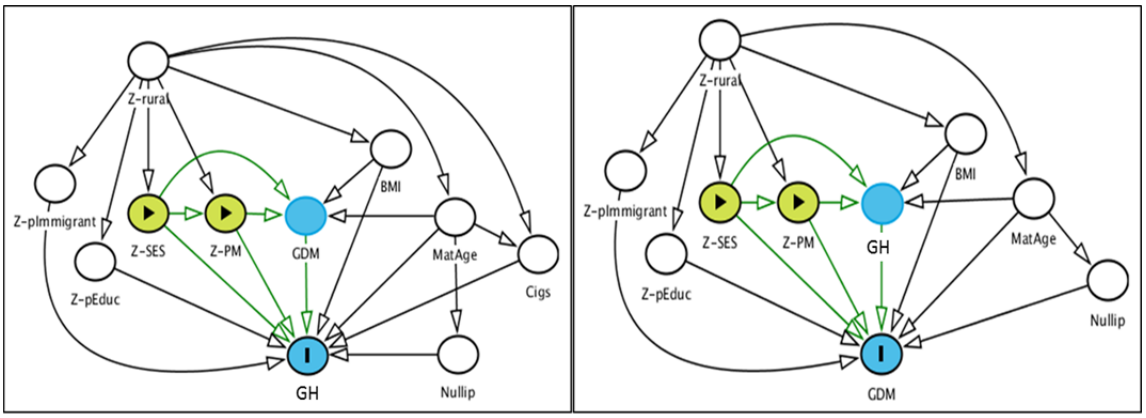

Figure 21: Directed Acyclic Graphs depicting the hypothesised relationships for GH and GDM

Table 13: Summary of population and neighbourhood characteristics, [n (%)]

Characteristic	GH 3,918 (2.4)	Total (n = 166,369)	GDM 11,306 (6.8)	Total (n = 165,727)
Level-1 (individual)				
Nulliparous	2,580 (65.9)	80,359 (48.3)	6,136 (40.7)	106,325 (45.5)
Maternal age				
<= 24 years	632 (16.1)	28,485 (17.1)	758 (6.7)	28,415 (17.2)
25 – 35 years	2,196 (56.1)	102,497 (61.6)	6,681 (59.1)	102,148 (61.6)
>= 36 years	1,090 (27.8)	35,387 (21.3)	3,867 (34.2)	35,164 (21.2)
BMI				
Under Wt (<18.5)	121 (3.1)	10,323 (6.2)	459 (4.1)	10,318 (6.2)
Normal Wt (18.5 – 24.9)	1,714 (43.8)	104,112 (62.6)	5,385 (47.6)	103,904 (62.7)
Over Wt (25 – 29.9)	1,056 (27.0)	33,570 (20.2)	2,879 (25.5)	33,378 (20.1)
Obese (>= 30)	1,027(26.2)	18,364 (11.0)	2,583 (22.9)	18,127 (10.9)
Gestational Diabetes	535 (13.7)	11,306 (6.8)	--	--
Pre-existing Diabetes	74 (1.9)	642 (0.4)	--	--
Gestational Hypertension	--	--	535 (4.7)	3,844 (2.3)
Drug or Alcohol Flag	90 (2.3)	3,679 (2.2)	131 (1.2)	3,666 (2.2)
Smoked during pregnancy	363 (9.3)	17,519 (10.5)	874 (7.7)	17,437 (10.5)
Fall or Winter Season	1,847 (47.1)	80,152 (48.2)	5,606 (49.9)	79,836 (48.2)
Level-2 (DA) Variables				
SESi*	-1.57 – 1.12	-1.36 – 1.16	-1.64 – 1.04	-1.36 – 1.16
Higher Education*	0.36 – 0.66	0.36 – 0.66	0.36 – 0.58	0.35 – 0.66
Immigrant Density*	0 – 0.50	0 – 0.47	0 – 0.52	0 – 0.47
Rural Address	257 (6.6)	13,920 (8.4)	416 (3.7)	13,871 (8.4)
On First Nation Reserve	29 (0.7)	1,694 (1.0)	74 (0.7)	1,687 (1.0)
$PM_{2.5}$ quintile				
Q1	595 (15.2)	33,257 (20.0)	1,491 (13.2)	33,124 (20.0)
Q2	659 (16.8)	33,277 (20.0)	1,765 (15.6)	33,145 (20.0)
Q3	752 (19.2)	33,277 (20.0)	2,419 (21.4)	33,158 (20.0)
Q4	949 (24.2)	33,268 (20.0)	2,683 (23.7)	33,138 (20.0)
Q5	963 (24.6)	33,290 (20.0)	2,948 (26.1)	33,162 (20.0)

Pre-existing Diabetes: indication of pre-existing diabetes mellitus (Type 1 or 2) or insulin-dependent diabetes mellitus; Drug or Alcohol Flag: physician indicated use of drugs (prescription, non-prescription, illicit) or alcohol as a risk factor in current pregnancy; Smoked: indication that the mother smoked at some point during the pregnancy; Fall or winter season of birth: Sept – Feb; Higher Education: proportion of population with any post-secondary education; Immigrant Density: proportion of population identified as immigrants from continental Asia (including Middle East and South Asia).*show the 10^{th} and 90^{th} percentiles.

Table 14: ORs for GH and GDM in relation to $PM_{2.5}$ and DA-level SES variables

	GH-RI-m1 N = 166,369 OR (95%CI)	GH-MI-m1 N = 234,776 OR (95%CI)	GDM-RI-m1 N = 165,727 OR (95%CI)	GDM-MI-m1 N = 233,842 OR (95%CI)
$PM_{2.5}$ quintile				
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	1.18 (1.05 – 1.33)	1.12 (1.00 – 1.25)	1.17 (1.08 – 1.27)	1.23 (1.14 – 1.33)
Q3	1.32 (1.17 – 1.49)	1.18 (1.06 – 1.33)	1.39 (1.28 – 1.50)	1.43 (1.33 – 1.55)
Q4	1.69 (1.51 – 1.91)	1.50 (1.34 – 1.67)	1.54 (1.42 – 1.68)	1.57 (1.45 – 1.70)
Q5	1.69 (1.50 – 1.91)	1.61 (1.44 – 1.81)	1.63 (1.50 – 1.78)	1.74 (1.61 – 1.89)
SESi	0.91 (0.88 – 0.94)	0.94 (0.91 – 0.98)	0.78 (0.76 – 0.80)	0.84 (0.82 – 0.86)
Higher Education	0.95 (0.92 – 0.99)	0.94 (0.91 – 0.97)	0.91 (0.89 – 0.94)	0.95 (0.93 – 0.98)
Immigrant Density	1.12 (1.09 – 1.16)	1.09 (1.06 – 1.12)	1.17 (1.15 – 1.20)	1.15 (1.13 – 1.18)
DA-mean BMI	1.04 (1.00 – 1.09)	--	1.09 (1.06 – 1.12)	--
Rural Residence*	--	--	0.56 (0.49 – 0.62)	0.57 (0.51 – 0.64)

The ORs for the three continuous DA-level variables correspond to a 1 standard deviation change from the mean. Models for GH adjusted for: maternal age, nulliparous, pre-existing diabetes, BMI, maternal smoking, drug flag; Models for GDM adjusted for: maternal age, nulliparous, BMI, drug or alcohol flag, First Nation on-reserve birth; MI-models additionally adjusted for imputed maternal education and imputed BMI, but not DA-mean BMI. * Due to the correlation between rural, $PM_{2.5}$ and SES, the ORs reported here are the direct effects of rural residence on GDM conditional on the other variables in the model. Rural was not significant for GH.

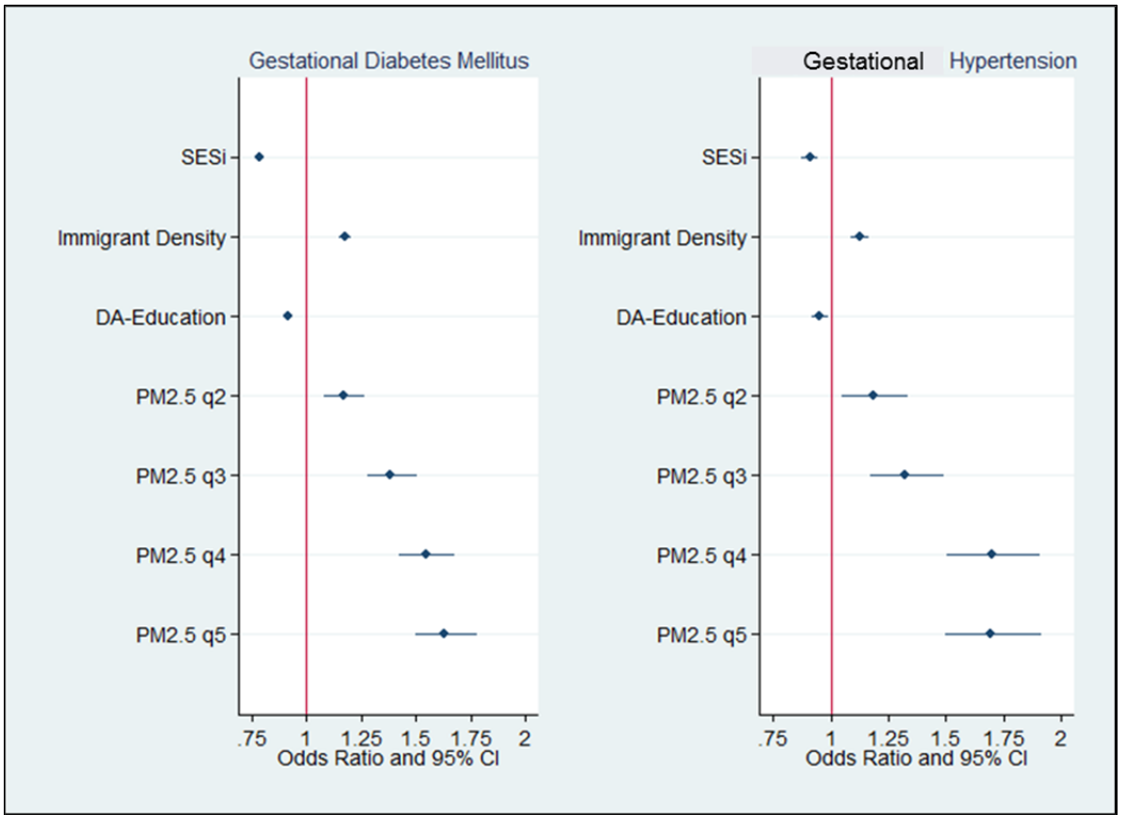

Figure 22: Adjusted ORs and 95% CIs for GDM and GH in relation to PM2.5 quintiles and DA-level SES variables

Table 15 reports the results from the interaction model between $PM_{2.5}$, SES and rural residence on GDM for both the random intercept and multiple imputed models. The results show that the dose-response association between the risk of GDM and increasing levels of $PM_{2.5}$ is present only for urban births and that the protective association of SES on GDM is also less pronounced in rural areas. These results are graphically presented in Figure 23 which clearly shows the stark contrast in effects between urban and rural births. The multiple imputed model shows slight changes in the magnitude of the ORs, but doesn't alter their direction or interpretations.

Table 16 reports the results from the interaction model between $PM_{2.5}$, SES and maternal BMI (above or below BMI = 25). The results are graphically presented in Figure 24 which show that living in higher SES neighbourhoods reduces the risk of GDM among higher BMI mothers as well as being protective against increased levels of $PM_{2.5}$. The interaction between BMI and $PM_{2.5}$ suggests that the effect of $PM_{2.5}$ on GDM is stronger among larger BMI mothers, but only among those living in lower SES DAs.

Table 15: ORs for gestational diabetes in relation to $PM_{2.5}$, SES, and Rural Residence

	GDM-RI-m2 SES*Rural*$PM_{2.5}$ OR (95%CI)	GDM-MI-m2 SES*Rural*$PM_{2.5}$ OR (95%CI)
$PM_{2.5}$ quintile		
Q1	1.00 (reference)	1.00 (reference)
Q2	1.32 (1.19 – 1.42)	1.40 (1.27 – 1.55)
Q3	1.59 (1.44 – 1.67)	1.72 (1.57 – 1.88)
Q4	1.72 (1.55 – 1.79)	1.85 (1.68 – 2.03)
Q5	1.83 (1.65 – 1.92)	2.05 (1.87 – 2.26)
SESi	0.93 (0.85 – 1.02)	0.93 (0.86 – 1.02)
Rural Residence	0.71 (0.59 – 0.84)	0.75 (0.63 – 0.89)
Rural*$PM_{2.5}$ quintile		
Rural*Q1	1.00 (reference)	1.00 (reference)
Rural*Q2	0.79 (0.60 – 1.05)	0.75 (0.58 – 0.98)
Rural*Q3	0.62 (0.42 – 0.91)	0.65 (0.47 – 0.90)
Rural*Q4	0.58 (0.33 – 1.05)	0.53 (0.35 – 0.81)
Rural*Q5	0.52 (0.28 – 0.97)	0.63 (0.46 – 0.86)
SESi*$PM_{2.5}$ quintile		
SESi*Q1	1.00 (reference)	1.00 (reference)
SESi*Q2	0.84 (0.75 – 0.94)	0.91 (0.82 – 1.02)
SESi*Q3	0.89 (0.80 – 0.99)	0.91 (0.83 – 1.01)
SESi*Q4	0.79 (0.72 – 0.88)	0.85 (0.77 – 0.93)
SESi*Q5	0.82 (0.74 – 0.91)	0.86 (0.78 – 0.94)
Rural*SESi	0.84 (0.72 – 1.00)	0.87 (0.76 – 1.00)
Model adjusted for: maternal age, nulliparous, BMI, drug or alcohol flag, DA-level education, DA-level Asian immigrant density, First Nation on-reserve birth; DA-mean BMI; Multiple imputed model additionally adjusted for		

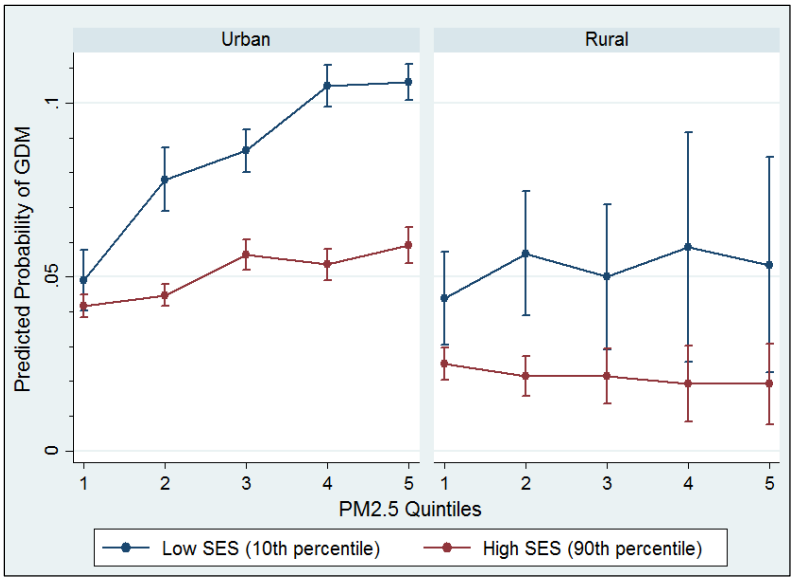

Figure 23: Predicted Probability of Gestational Diabetes Mellitus with 95%CIs in relation to $PM_{2.5}$, SES and Rural Residence

Table 16: ORs for gestational diabetes in relation to $PM_{2.5}$, SES, and maternal BMI[a]

	GDM-RI-m3 SES*BMI*$PM_{2.5}$ OR (95%CI)	GDM-MI-m3 SES*BMI*$PM_{2.5}$ OR (95%CI)
$PM_{2.5}$ quintile		
Q1	1.00 (reference)	1.00 (reference)
Q2	1.32 (1.16 – 1.51)	1.35 (1.23 – 1.49)
Q3	1.70 (1.50 – 1.93)	1.69 (1.54 – 1.86)
Q4	1.91 (1.68 – 2.17)	1.87 (1.69 – 2.07)
Q5	2.00 (1.76 – 2.28)	2.13 (1.90 – 2.38)
BMI (≥ 25)	2.83 (2.52 – 3.16)	2.69 (2.40 – 3.01)
SESi	0.87 (0.79 – 0.95)	0.87 (0.80 – 0.95)
BMI*SESi	1.06 (1.02 – 1.11)	1.04 (1.00 – 1.09)
DA-mean BMI	1.12 (1.09 – 1.16)	1.11 (1.09 – 1.14)
SESi*$PM_{2.5}$		
SESi*Q1	1.00 (reference)	1.00 (reference)
SESi*Q2	0.86 (0.77 – 0.96)	0.95 (0.85 – 1.05)
SESi*Q3	0.92 (0.83 – 1.02)	0.95 (0.86 – 1.05)
SESi*Q4	0.83 (0.75 – 0.92)	0.88 (0.80 – 0.97)
SESi*Q5	0.86 (0.78 – 0.95)	0.90 (0.82 – 0.99)
BMI*$PM_{2.5}$		0.95 (0.92 – 0.98)†
BMI*Q1	1.00 (reference)	
BMI*Q2	0.93 (0.80 – 1.08)	
BMI*Q3	0.81 (0.70 – 0.93)	
BMI*Q4	0.75 (0.65 – 0.86)	
BMI*Q5	0.77 (0.66 – 0.88)	

[a] BMI transformed to dichotomous variable (overweight or obese, BMI≥25); Model adjusted for: maternal age, nulliparous, drug or alcohol flag, Rural residence, DA-level education, DA-level Asian immigrant density, First Nation on-reserve birth; Multiple imputed model additionally adjusted for maternal education. N = 165,727 for GDM-M3-ri; N = 233,842 for GDM-M3-mi; † interaction using imputed continuous interaction variable.

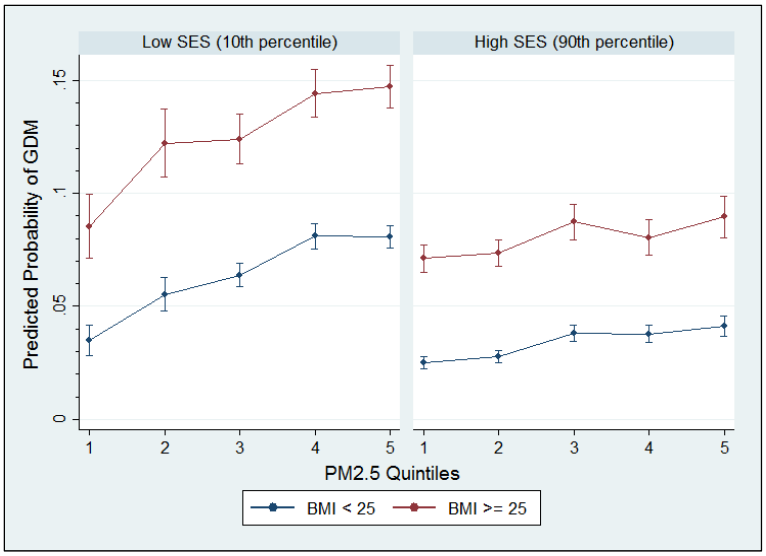

Figure 24: Predicted Probability of Gestational Diabetes Mellitus with 95%CIs in relation to $PM_{2.5}$, SES and BMI

The DA-level random intercept variance, MOR, explained proportional change in variance (PVC), model diagnostics (AIC) and spatial effects are presented in Tables 17 and 18 for GH and GDM respectively. In Table 17 for the GH models, the MOR and 95% CI for the Null random intercept model was 1.39 (1.30 – 1.50), indicating that a randomly selected individual would experience, in median, a 40% increase in their risk of GH moving from a low risk DA to a higher risk DA. The addition of the level-1 covariates increased the MOR to 1.45 likely due to the increase in the level-2 random intercept variance (0.119 to 0.151). Including the DA-level SES and $PM_{2.5}$ variables partially addressed the DA-level variance, resulting in a cumulative PCV of 11.3% and 32.1% respectively compared to the Null model. The MOR was reduced to 1.31 (1.22 – 1.45) for the final model, signifying that a good deal of significant between-area heterogeneity in the risk of GH remained. Similar trends were seen in Tables 18 for the GDM models, but with larger DA-level random effects. The MOR and 95% CI for the Null random intercept model was 1.62 (1.57 – 1.67) which was reduced to 1.38 (1.33 – 1.43) in the final models. The addition of the SES and $PM_{2.5}$ variables resulted in a cumulative PCV of 46% and 55% respectively, a considerable reduction in the DA-level variance. The inclusion of the interaction effects addressed a small additional amount of variance; however, a significant amount of DA-level heterogeneity remained unexplained.

Table 17: Random effects and model diagnostics from hierarchical logistic models for GH in BC, Canada

Random Effects & Model Diagnostics	Null Model	Level-1 Model	Level-2 (+SES)	Level-2 (+$PM_{2.5}$)
Intercept	0.023	0.008	0.008	0.006
RI variance	0.119	0.151	0.106	0.081
PCV (%)	Ref.	-26.9	11.3	32.1
MOR (95%CI)	1.39 (1.30 – 1.50)	1.45 (1.36 – 1.56)	1.36 (1.28 – 1.49)	1.31 (1.22 – 1.45)
AIC	37094	35155	35033	34936
Moran's I^{κ}	--	0.090	--	0.049

RI variance: random intercept variance; MOR: Median odds ratio; AIC: Akaike Information Criterion; PCV: proportional change in variance expresses the cumulative change in the DA-level variance between the corresponding model and Null model; Moran's *I*: Local Moran's *I* for spatial autocorrelation, all results were significant p<0.01 with 999 permutations using a nearest neighbor (knn=7) spatial weight matrix.

Table 18: Random effects and model diagnostics from hierarchical logistic models for GDM in BC, Canada

Random Effects & Model	Null Model	Level-1 Model	Level-2 (+SES)	Level-2 (+$PM_{2.5}$)	GDM-M2-ri (SES-Rural-$PM_{2.5}$)	GDM-M3-ri (SES-BMI-$PM_{2.5}$)
Intercept	0.064	0.039	0.042	0.032	0.028	0.026
RI variance	0.255	0.295	0.137	0.115	0.110	0.112
PCV (%)	Ref.	-15.7	46.3	55.0	56.6	56.1
MOR (95%CI)	1.62 (1.57 – 1.67)	1.68 (1.63 – 1.73)	1.42 (1.38 – 1.47)	1.38 (1.34 – 1.43)	1.37 (1.33 – 1.42)	1.38 (1.33 – 1.43)
AIC	81917	77576	76579	76427	76410	76834
Moran's I^{κ}	--	0.281	--	0.098	--	--

See Table 17 caption of abbreviation definitions.

Spatial analyses were used as a model diagnostic to test for significant spatial autocorrelation of model residuals using the level-2 predicted random intercepts. The local Moran's *I* statistics reported in Tables 17 and 18 for the Level-1 models indicate the presence of local spatial clustering between neighbourhoods, particularly for GDM. The addition of level-2 variables reduced the Moran's *I* substantially; however, small but significant clustering remained for both GH and GDM (Figures 25 and 26). Spatial lag models further confirmed the statistical significance of the DA-level variables while accounting for spatial dependence in the dependent (y) variable. A statistically significant

spatial lag coefficient (rho, ρ) indicates that the intercept value for a given focal DA covaries with that of its neighbours. Spatially-lagged versions of $PM_{2.5}$ and SESi were added to the spatial lag models for GH and GDM to test the influence of the values of the neighbouring units on the focal DA. While significant, they only slightly reduced the rho coefficient (0.22 to 0.21) indicating residual spatial dependence of the dependent variable with its contiguous neighbours.

Further sensitivity analyses using only the non-imputed DAs showed very minor differences in magnitude of significant variables in both the GH and GDM models. As an additional sensitivity test, abnormal glucose factor (AGF) was used as an outcome as pre-diabetes indicator. The magnitude and direction of the DA-level variables were similar to those for GDM shown in Table 14, with the exception of $PM_{2.5}$. Higher levels of $PM_{2.5}$ were shown to have a strong dose-dependent association with risk of AGF, OR (95% CI) Q2 vs. Q1: = 1.52 (1.30 – 1.78) and Q5 vs. Q1: 2.41 (2.06 – 2.82). Similar heterogeneity was present between SES, $PM_{2.5}$ and rural residence for AGF as it was for GDM; however, unlike GDM, the interaction between BMI, SES and $PM_{2.5}$ was not significant.

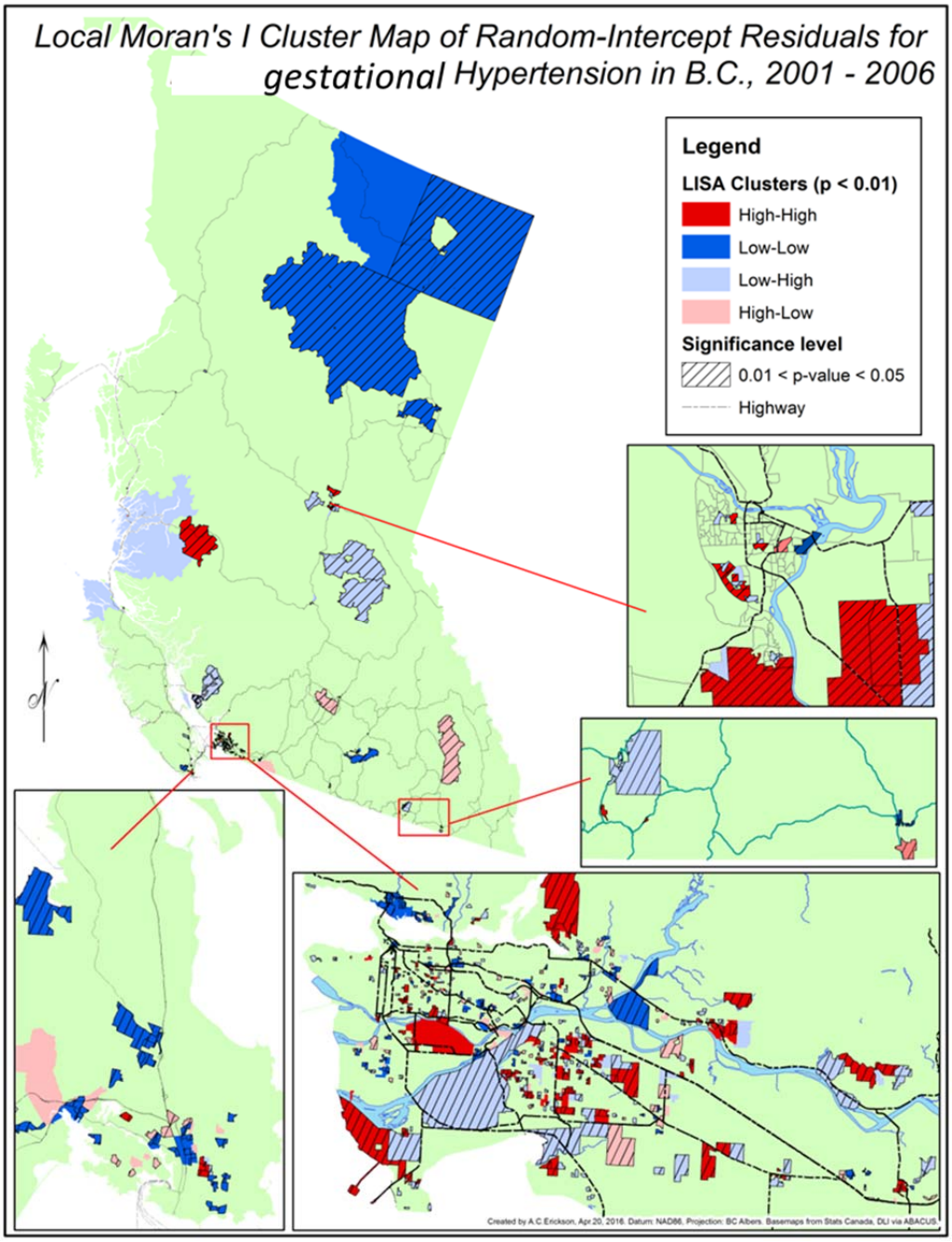

Figure 25: Clusters and Outliers of Localized Spatial Autocorrelation in DA-level (random intercept) Residuals for Gestational hypertension in B.C., 2001 – 2006

This map shows the localized spatial autocorrelation (clustering) of the random intercept residuals after adjustment for the individual and DA neighbourhood-level variables. Areas in dark red indicate DA clusters where the model under-predicted the risk of GH, while areas in dark blue indicate DA clusters where the model over-predicted the risk of GH. The lighter shades of blue and red indicate spatial outliers where low areas are next to high and high next to low, respectively. Significance was estimated using 99,999 Monte Carlo simulations, and area without cross-hatching indicate areas where the probability of type I error was less than 0.01.

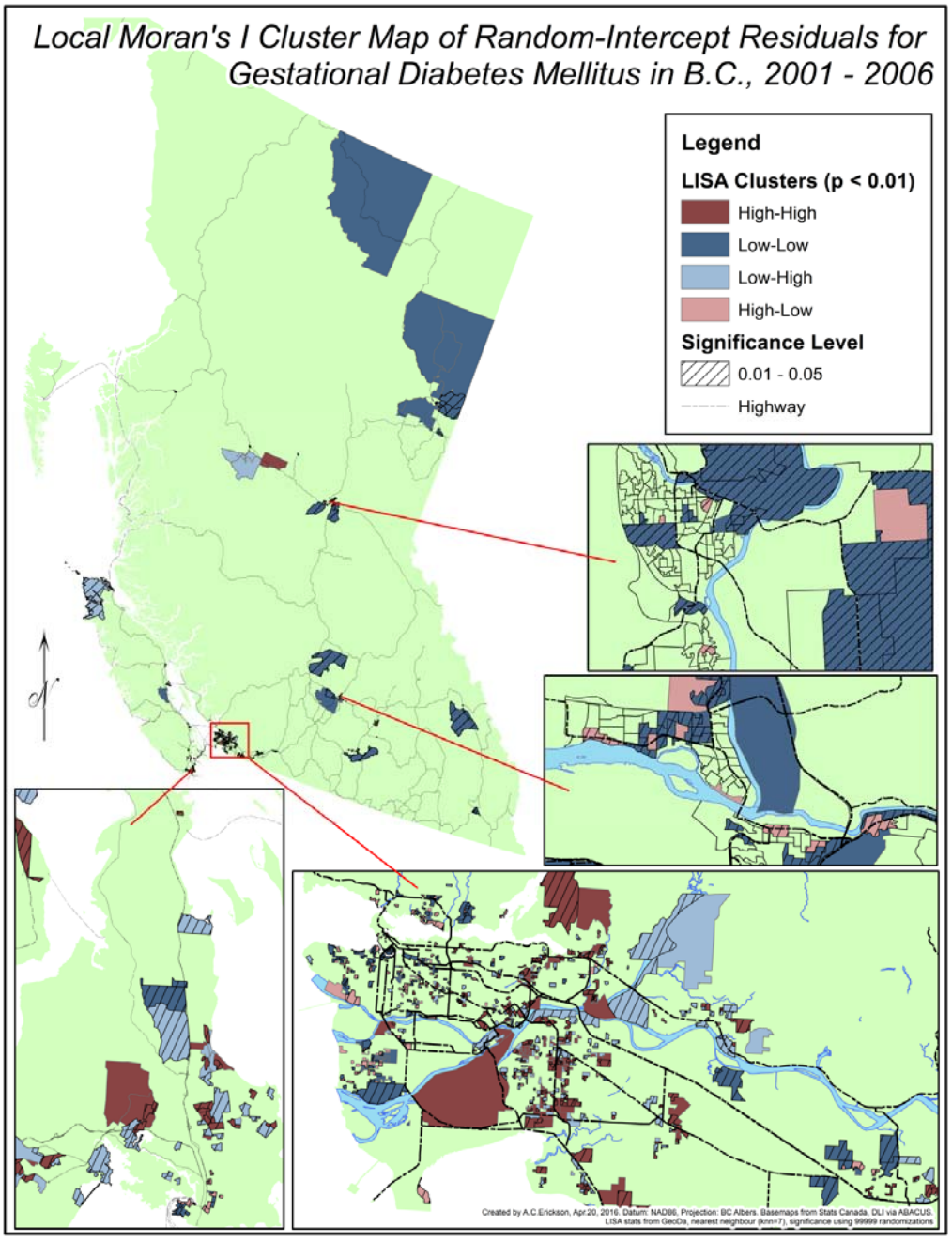

Figure 26: Clusters and Outliers of Localized Spatial Autocorrelation in DA-level (random intercept) Residuals for Gestational Diabetes Mellitus in B.C., 2001 – 2006

This map shows the localized spatial autocorrelation (clustering) of the random intercept residuals after adjustment for the individual and DA neighbourhood-level variables. Areas in dark red indicate DA clusters where the model under-predicted the risk of GDM, while areas in dark blue indicate DA clusters where the model over-predicted the risk of GDM. The lighter shades of blue and red indicate spatial outliers where low areas are next to high and high next to low, respectively. Significance was estimated using 99,999 Monte Carlo simulations, and area without cross-hatching indicate areas where the probability of type I error was less than 0.01.

4.0 Discussion

This study employed multilevel random intercept logistic regression models to assess the association of $PM_{2.5}$ and SES-related neighbourhood factors on the risk of GH and GDM in BC for the years 2001 to 2006. It is important to note that the GH variable used in this study only identifies pregnancies where hypertension was measured, regardless of timing of onset (i.e. previous chronic or gestational). Regardless, our results show a consistent dose-response association in the risk of GH and GDM with increasing levels of $PM_{2.5}$. Higher DA-level SES and education were associated with lower risks for both GH and GDM, while higher immigrant density and higher DA-mean BMI showed an increased risk. However, only GDM showed considerable effect heterogeneity, particularly in urban areas where the interaction between $PM_{2.5}$ and SES greatly modified the risk of GDM (Figure 23). Furthermore, these associations are potentially more pronounced among mothers with larger pre-pregnancy BMI (Figure 24). The use of random intercept models revealed that there was a moderate degree of individual-level clustering within neighbourhood DAs and significant between-DA variability in the risk of GH and GDM. While this DA-level intercept variance was largely explained with the inclusion of the DA-level SES and $PM_{2.5}$ variables, some variance remained and was shown to be, at least partially, spatially clustered at a local scale. This latter observation suggests the presence of other unmeasured DA-level variables that could be causing the intercept residuals to cluster.

Our results corroborate the growing literature supporting the association between $PM_{2.5}$ exposure and the risk of GH and GDM [9,10,13–15]. Studies that tested different air pollutants (NO_2) or used proximity to roads as the exposure measure also found significant risks of GDM and hypertensive disorders, including preeclampsia [11,68–70]. We also found an association between $PM_{2.5}$ and the pre-diabetic indicator of abnormal glucose factor (AGF), a result found by Fleisch et al as well [71]. While the link between $PM_{2.5}$ and non-pregnancy hypertension and cardiovascular injury is well established [21,72], there is mounting evidence of an association between air pollution (NO_2 and $PM_{2.5}$) and type II diabetes [16,27,29,73]. Lui et al [27] reviewed the hypothesized mechanisms of $PM_{2.5}$ mediated diabetes/insulin resistance, which has several overlapping pathways with the hypothesized mechanisms of $PM_{2.5}$ mediated cardiovascular injury and gestational hypertensive disorders [19,20]. These include endothelial dysfunction, endoplasmic reticulum stress-induced apoptosis, and altered mitochondrial morphology and function largely induced by systemic inflammation and oxidative stress [19,27,74].

Our results show effect heterogeneity between $PM_{2.5}$ and SES on the risk of GDM such that those residing in lower SES neighbourhoods showed a more pronounced effect of increased levels of $PM_{2.5}$, but only in urban areas (Figure 23). The significant interaction between rural address and $PM_{2.5}$ may reflect the underestimation of $PM_{2.5}$ in rural areas by the LUR model [53]. The composition of $PM_{2.5}$, and thus its relative toxicity, is shown to vary spatially depending on its source (e.g. wood smoke vs. traffic-related emissions) and may partially explain the observed rural-urban differences [19,23]. Lower SES has been associated with an increased risk of GDM in Canada [3,75], and disparities in birth outcomes by neighborhood indicators of SES are often more pronounced in urban versus rural areas due to greater income inequality [76,77]. Other explanations could be due to access to care and the underdiagnoses of type II diabetes in rural areas [78], or that the prevalence of GDM is lower in rural compared to urban areas in Canada [7,79].

We also observed significant effect heterogeneity between $PM_{2.5}$, SES and maternal BMI (Figure 24). These results show that the effect of $PM_{2.5}$ on the risk of GDM is greater on mothers who had a pre-pregnancy BMI of 25 and above, but only among those in lower SES neighbourhoods. This suggests that not only can neighbourhood characteristics influence the risk of GDM but can also modify exposure effects and are conditional on maternal characteristics. It's been shown that obesity may enhance the associations between $PM_{2.5}$ and systematic inflammation [80], therefore mothers with larger pre-pregnancy BMIs may be more susceptible to the effects of air pollution when compounded by other neighbourhood-level stressors.

The application of multilevel models in perinatal epidemiology has become more common, demonstrating the importance of neighbourhood and community-level context in the health of individuals [38,81]. By permitting the intercept to vary randomly between the neighbourhood-level units, it is possible to quantify the magnitude the neighbourhood-level factors have on addressing the between-area variability. Furthermore, specific to logistic multilevel models, computing the median odds ratio (MOR) permits the expression of the neighbourhood-level variance on the OR scale thereby permitting the direct comparison of the magnitude of the area-level variance with that of the model covariates [62]. For example, in the present study the MOR (95% CI) for the Level-2 model for GDM adjusted for the SES variables and $PM_{2.5}$ was 1.38 (1.34 – 1.43), signifying that in the median case the residual heterogeneity between DAs will increase the risk of GDM by 38% when randomly selecting two people in different areas. Therefore, a person's residential neighbourhood is

of greater relevance to their risk of GDM than some maternal-level factors and on par with some DA-level factors such as DA-mean BMI, immigrant density, and being in the 3rd exposure quartile for $PM_{2.5}$. Despite explaining a substantial proportion of the between-DA variance, there remained unmeasured neighbourhood-level processes producing between neighbourhood differences in GH and GDM risk.

We used spatial analyses to examine whether the remaining DA-level heterogeneity was clustered spatially at the local scale as well as a serving as a measure of model specification and how well the chosen representative neighbourhood (DA) unit performed. While the inclusion of the DA-level variables substantially reduced the spatial autocorrelation in the random intercept variance (Moran's *I* in Tables 17 and 18), there remained some significant spatial autocorrelation for both GH and GDM (Figures 25 and 26). This could suggest that some unmeasured spatial process is occurring at the local level, misspecification with respect to an unmeasured covariate risk factor, and/or the use of DAs as the neighbourhood spatial unit being less optimal to assess the neighbourhood-level effects. Testing this last point, we found that spatially lagged versions of $PM_{2.5}$ and SES were significant in spatial lag regression models for GH and GDM respectively. This suggests the possible presence of spatial externalities in which neighbouring values of these variables influence the risk of GH or GDM in the focal neighbourhood [82,83].

A key component of this research was the use of a land-use regression (LUR) model of air pollution [53]. While the LUR model was independently validated and achieved decent overall results in its predicted estimates, the very nature of our study design ensures some degree of exposure misclassification to our study population, although it is expected to be non-differential. These limitations include the occurrence of maternal intra-urban commuting and potential inter-urban relocation within the pregnancy period, the cross-sectional nature of the $PM_{2.5}$ LUR model based on 2006 air quality monitoring data while the study period of our perinatal dataset spans 6 years (2001 to 2006) and, finally, that the LUR $PM_{2.5}$ concentrations may be under-predicted with have less variability compared to compiled monitored air quality data [84].

The strengths of this study include a large population-based cohort in order to test for potential effect heterogeneity, good control for maternal-level confounders such as smoking, pregnancy history, and BMI, and the ability to link to and assess neighbourhood-level socioeconomic and demographic contextual factors that influence the disease outcomes. Furthermore, the use of multiple imputation models for the missing BMI as well

as maternal education data further substantiated the main findings. The calculation of the MOR from the random intercept variance term and use of spatial analyses show that local neighbourhood factors are important in reproductive health and further efforts to understand their role should be prioritized.

5.0 Conclusions

This study supports the growing literature of the effect of $PM_{2.5}$ on the risk of GH and GDM and provides new insights into the role neighbourhood-level SES and demographic factors play. With respect to GDM, higher SES neighbourhoods had a strong protective effect against $PM_{2.5}$ exposure in urban areas while at the same time were also shown to temper the negative effect of larger maternal BMIs on GDM risk. The use of spatial analyses indicates that unmeasured localized processes are responsible for the unexplained between-neighbourhood heterogeneity, and the communication using risk maps may inform public health and municipal planners on possible mechanisms to target improvements. The implications of a potential link between GH and GDM with $PM_{2.5}$ exposure are profound as this air pollutant is pervasive throughout the world, and therefore even modest mitigation in exposure will provide substantial public health benefits.

6.0 References

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Chapter 7: Conclusions

1.0 Introduction

On October 1, 2015, the International Federation of Gynecology and Obstetrics (FIGO) announced its ground-breaking policy statement on environmental health regarding the need to reduce and prevent the reproductive health impacts from exposure to toxic environmental chemicals [1]. As the leading voice of reproductive health professionals worldwide, this stance by FIGO has profound global resonance.

The objective of this dissertation was to examine how factors of the social and physical environment influence the risk of adverse pregnancy outcomes and whether they interact with each other or with maternal characteristics to modify disease risk. Each research chapter in this thesis was designed for independent publications and contains specific conclusions, contributions and limitations. Therefore, this final chapter serves to synthesize the overall findings and key contributions, highlight overall limitations of the research, and propose future research directions.

2.0 Summary of Research and Contributions

This dissertation contributed to the literature as well as to public and population health through: (1) the use of heavy maternal smoking during pregnancy as a marker for unmeasured SES-related lifestyle risk factors that influence birth outcomes; (2) creating new epidemiological evidence regarding the variability in the effect of maternal smoking on birth weight and how maternal and neighbourhood-level factors can exasperate or attenuate its effect; and (3) corroborating the growing epidemiological knowledge concerning $PM_{2.5}$ exposure and adverse pregnancy outcomes and its interaction with neighbourhood SES and demographic variables.

2.1. Heavy smoking as a marker for unmeasured SES-related lifestyle risk factors

Maternal smoking remains one of the most important modifiable risk factors, with potential implications on subsequent child development and health. The results of this large population-based study find that smoking during pregnancy is a modifiable dose-dependent risk factor of adverse fetal growth that also has a strong relationship with other risk behaviours and indicators of low SES. These results also reinforce the importance of the standardized and complete collection of SES variables for *all* patients by perinatal health care providers. The impact of this paper on the public health literature is notable, being

designated as a "high access" article on the BMC Public Health website and being referenced 45 times in other peer-reviewed and other academic works.

Compared to all lower levels of smoking, heavy smokers (≥ 10 cigarettes/day) had substantially worse birth outcomes and were also at increased risk to be flagged for alcohol or drug use, be a single parent, attend fewer prenatal care visits, and to have a pre-pregnancy weight greater than 74 kilograms. Heavy smokers were 3.8 times more likely to have not graduated high school compared with moderate, light and non-smokers combined. Furthermore, the addition of the behavioural and SES indicator variables, particularly maternal education, explained some or all of the risk attributed to light smoking but heavy smoking remained a strong marker of increased risk for impaired fetal growth.

This supports the possibility that reports of smoking greater than ten cigarettes per day might be an early marker for the need for comprehensive supports to reduce adverse outcomes. In BC, this would identify approximately five percent of women at particular increased risk of adverse outcomes that may benefit from additional services to promote a healthy pregnancy. The ability to recognize those at particular risk early in pregnancy and provide preventative programs could help achieve better outcomes for all expectant mothers. While strategies for smoking cessation are important and supported by our study, the underlying issues that lead to adverse birth outcomes might not be addressed with a narrow focus (demonstrated by the results in Chapter 5). This information may be used for planning targeted intervention programs not only for smoking cessation but potentially other maternal support services such as nutrition and healthy pregnancy education with the overall goal of optimizing birth outcomes. Antenatal care is a critical access point for the education of expectant mothers regarding a healthy pregnancy, particularly for first-time mothers, who may be more amenable to smoking cessation and other healthy lifestyle changes.

2.2 Effect modification of maternal smoking on birth weight by neighbourhood-level factors

New and important epidemiological findings were reported in this dissertation on the ability of neighbourhood-level factors to modify the negative effects of maternal smoking on birth weight.

The assumption that maternal smoking affects all pregnancies equally, while safe in itself, may not capture important insights into possible cessation interventions. The results in Chapter 5 show that the effect of maternal smoking on birth weight is not constant across geography, but depends on the social and physical environment. The use of random

coefficient models revealed neighbourhood-level differences in how maternal smoking negatively impacted birth weight and demonstrated effect modification by neighbourhood and maternal-level factors. The inclusion of the DA-level SES, demographic and $PM_{2.5}$ variables explained 68.5% of the random intercept variability in DA-mean birth weight. However, the random slope variability of maternal smoking on birth weight was only partially explained by the cross-level interactions suggesting the presence of other contextual neighbourhood-level factors.

Our analyses confirm previously shown modification of the smoking-birth weight relationship by maternal risk factors; however, to our knowledge this is the first study to show that neighbourhood-level factors are able to modify this relationship. We found a significant negative interaction between cigarettes/day and neighbourhood-level SESi. This suggests that maternal smoking may have little relevance in affecting birth weight in very low SES neighbourhoods, but becomes more prominent as neighbourhood-level SES increases when perhaps other stressors negatively impacting birth weight are reduced.

Higher proportions of neighbourhood-level post-secondary education had positive interaction with cigarettes/day suggesting that heavy smokers may benefit the most by living in higher educated neighbourhoods. Explanations could be that smoking cessation rates in pregnancy are higher in better educated neighbourhoods where healthier behaviours are more common. Neighbourhood social supports and transmission of behaviours could also explain the observed positive interaction with higher immigrant density and may reflect the buffering effect of strong community cohesiveness and beneficial cultural practices. Conversely, the observed negative interaction between rural address and cigarettes/day could be due to the transmission of negative behaviours being more common, and where less support for cessation may lead to smoking throughout pregnancy.

The buffering effect of $PM_{2.5}$ with increased levels of maternal smoking is curious but could provide evidence for a protective pre-conditioning stress that activates an adaptive response and increases biological resistance to cigarette-induced harms. Hence interventions focusing exclusively on individual behaviours may have limited success without addressing the contextual influences at the neighbourhood-level.

2.3 Epidemiological findings

2.3.1 The interaction between $PM_{2.5}$ and neighbourhood SES variables on birth weight and measures of adverse fetal growth.

The main environmental factors examined include ambient particulate air pollution ($PM_{2.5}$), neighbourhood socioeconomic status (SES), neighbourhood immigrant density, neighbourhood level of post-secondary education level and the urban-rural context. The results show that individual and neighbourhood-level factors are capable of modifying the association between $PM_{2.5}$ exposure and fetal growth. Furthermore, through the use of random-slopes models we show that the effect of gestational age on birth weight can vary considerably between neighbourhoods.

These results show a small negative interaction between $PM_{2.5}$ and SES such that a more pronounced effect of $PM_{2.5}$ was seen in lower SES neighbourhoods; however this result appears for births in urban areas only. The protective interaction with higher immigrant density on $PM_{2.5}$ exposure shows that not only can neighbourhood characteristics influence fetal growth but that they can also modify exposures either positively or negatively.

Interactions between $PM_{2.5}$ and maternal-level variables shown to reduce birth weight independently revealed some counter-intuitive results. While further studies are needed to confirm these findings, the persistence of the results after various sensitivity analyses suggests a hypothesis that some individual-level exposures may act as a pre-conditioning stress that activates an adaptive response of increased biological resistance to similar or other stressors. A protective effect of older maternal age against $PM_{2.5}$ exposure was also observed and may stem from increased nutritional awareness among older women and/or more secure income and support networks thereby reducing potential stress and anxiety. Pregnancies affected by gestational diabetes had significantly higher birth weights as expected but revealed a sharp reduction in birth weight with increasing $PM_{2.5}$.

Our results corroborate the growing literature supporting a negative association between $PM_{2.5}$ and birth weight in a setting of relatively low air pollution concentrations. This strengthens the evidence of the low-dose effects of $PM_{2.5}$. Furthermore, this study supports the growing literature of an effect of $PM_{2.5}$ on fetal growth and its modification by both maternal and neighbourhood-level factors. Most notably, it shows that lower SES neighbourhoods may be more negatively affected by higher levels of $PM_{2.5}$, but only in urban areas.

2.3.2 $PM_{2.5}$ exposure increases the risk of gestational diabetes mellitus (GDM) and gestational hypertension (GH).

This study supports the growing literature of an effect of $PM_{2.5}$ on the risk of GH and GDM and provides new insights into the role of neighbourhood-level SES and demographic factors have on their prevalence. Our results show a consistent dose-response association in the risk of GH and GDM with increasing levels of $PM_{2.5}$. Higher DA-level SES and education were associated with lower risks for both GH and GDM, while higher immigrant density and higher DA-mean BMI showed an increased risk. Further, higher SES neighbourhoods had a strong protective effect against $PM_{2.5}$ exposure for the risk of GDM in urban areas while also shown to temper the negative effect of larger maternal BMIs on GDM risk.

The median odds ratio (MOR) permits the expression of the neighbourhood-level variance on the OR scale thereby permitting the direct comparison of the magnitude of the area-level variance with that of the model covariates. The MOR (95%CI) for the adjusted level-2 model for GDM was 1.38 (1.34 – 1.43), signifying that in the median case, a randomly selected individual moving from a low risk DA to a higher risk DA will realize a 38% increased risk of GDM. Thus, after adjusting for individual and neighbourhood-level known risk factors, a person's residential neighbourhood still exhibits a greater relevance to their risk of GDM than many of the measured model variables.

The use of spatial analyses indicates that unmeasured localized processes are responsible for the unexplained between-neighbourhood heterogeneity, and the communication using risk maps may inform public health and municipal planners on possible mechanisms to target improvements. The implications of a potential link between GH and GDM with $PM_{2.5}$ exposure are profound as this air pollutant is ubiquitous, and therefore even modest mitigation in exposure will provide substantial public health benefits.

3.0 Limitations

3.1 Use of DAs as neighbourhoods

We used spatial analyses to examine whether the remaining DA-level heterogeneity in the models was clustered spatially at the local scale which served as a measure of model specification as well as how well the chosen representative neighbourhood (DA) unit performed. In most cases, the inclusion of the DA-level variables substantially reduced the spatial autocorrelation in the random intercept variance indicating that the DAs performed well to capture the underlying spatial heterogeneity. However, there remained some significant spatial autocorrelation for some of the pregnancy outcomes, particularly GH and

GDM. This could suggest that some unmeasured spatial process is occurring at the local level, misspecification with respect to an unmeasured covariate risk factor, and/or the use of DAs as the neighbourhood spatial unit being less optimal to assess the neighbourhood-level effects for these outcomes. The addition of other neighbourhood-level variables such as green space and neighbourhood walkability score would be a possible avenue to explore first.

3.2 The $PM_{2.5}$ Land-use Regression Model

A key component of this research was the use of a land-use regression (LUR) model of air pollution. While the LUR model was independently validated and achieved decent overall results in its predicted estimates, the very nature of our study design ensures some degree of exposure misclassification in our study population. Our analysis was based on maternal place of residence at delivery, and therefore intra-urban commuting and potential inter-urban relocation within the pregnancy period was not accounted for which could affect the results. Time-activity patterns show that pregnant women spend more time at home in the later stages of pregnancy, but mobility patterns may differ by age, parity and SES.

Another limitation regarding the $PM_{2.5}$ exposure assessment is that the LUR model is cross-sectional based on 2006 air quality monitoring data, while the study period of our perinatal dataset spans 6 years (2001 to 2006). We therefore assume all pregnancies were exposed to the same levels of $PM_{2.5}$ for their entire pregnancy, regardless of their year of birth, based on their residential DA. This method also assumes that air pollution levels have remained relatively consistent with no inter-regional variation between the years. Air Zone reports from the BC Ministry of Environment show that while the average levels of $PM_{2.5}$ across BC have generally declined over the years from 2004 to 2006, inter-regional variation has also remained fairly consistent in the rate of decrease which will reduced the amount of potential exposure misclassification [2]. The use of this $PM_{2.5}$ LUR model also prevents the assessment of exposure windows by trimester, spatiotemporal studies of $PM_{2.5}$ have shown little to no difference between trimester-specific and entire pregnancy effects on birth weight. Finally, the mean $PM_{2.5}$ concentrations may be underestimated by the LUR model with less variability and missing several high $PM_{2.5}$ outlier locations in BC compared to compiled monitored data. This could potentially result in an underestimation of our observed association of reduced birth weight with increasing $PM_{2.5}$ levels.

Although direct comparisons to other studies are difficult to make due to our estimation of non-linear effects, substantially greater differences are seen in my results, especially in Chapter 3. This is largely due to my control for the proportion of neighbourhood Asian immigrant density and the use of a sequential regression procedure to remove the collinearity between immigrant density and $PM_{2.5}$ and SESi. Recall that a residualized or orthogonal variable for immigrant density (as well as proportion of higher education) was created in order to disentangle the direct effects of $PM_{2.5}$ and SES from immigrant density shown to be moderately correlated (r = 0.53 and 0.63 respectively). When models were run that used the non-transformed variables, the estimated associations between birth weight and $PM_{2.5}$ are reduced by approximately half (-9.9 grams, 95% CI = -12.8 to -7.1); however, despite the large change in effect size for $PM_{2.5}$ on birth weight, all relationships and interactions with other parameters remained unchanged and statistically significant. This smaller effect size is more similar to other studies of $PM_{2.5}$ on birth weight (see the supplementary tables for [3,4]). More methodological work needs to be done in future studies in order to correct for correlated confounding variables in order to estimate true direct effects.

In a recent paper by Gehring et al. (2014) that looked at the impact of noise and air pollution on pregnancy outcomes in Metro Vancouver BC Canada, a sub-region covered by my study that also used BCPDR data, they found that noise exposure was largely responsible for the negative associations with term birth weight in joint models arguing that noise could be the predominant exposure [3]. Their adjusted mean difference association between $PM_{2.5}$ and term birth weight was -3.1 grams (95%CI = -5.1 to -1.1), whereas for the transportation noise exposure it was -19.1 grams (95% CI = -22.9 to -15.3). Combined, their estimated mean differences are very similar to the associations presented in Chapter 3. If their conclusions are shown to be true by further research, it could be that our estimated $PM_{2.5}$ associations are confounded by unmeasured noise exposure. In urban areas, this effect will be very difficult to separate from air pollution given that both these exposures are largely driven by local vehicle traffic. Studies with a special focus on comparing populations living close to chronic point sources of noise will be needed to disentangle these effects.

3.3 Missing Data

We were unable to control for maternal-level SES, and therefore the neighbourhood-level effect estimates and interactions could reflect individual-level differences. Maternal

education is a variable provided in the BC Perinatal Data Registry, but was only available for 10% of our population. In Chapter 6, maternal education was included in the analysis using a statistically accepted multiple imputation technique with results showing that while maternal education was protective in itself for the risk of GDM and GH, it did not alter the overall DA-level associations. As we showed in Chapter 3, the adjustment for socially-patterned behavioural risk factors such as maternal smoking, suspected drug or alcohol use and few prenatal care visits will control for some individual-level SES differences.

3.4 First Nations Births

Health outcome research and surveillance of Aboriginal births in Canada is a complex and challenging endeavour. First Nations in Canada make up about 4% of the population, but is the fastest growing sub-population in Canada. First Nations people are increasingly living in cities or off-reserves, some by choice and some by necessity. Reproductive health surveillance is as important in First Nations of BC, as in mainstream BC, to ensure that evidence-based policies and supports are targeted to areas where they can have the most beneficial impact for healthy maternal and child health outcomes [5,6].

This research was largely funded by a CIHR Institute of Aboriginal Health Priority initiative although it was peer reviewed by the Children's health committee. The start of this project occurred during the transition to the First Nations Health Authority (FNHA). Dr. Arbour and I held three meetings with various representatives from the research arm of the organization that later became the FNHA. Given that there were no specific processes in place at that time for population epidemiology studies such as ours, we were provided with the information that individual First Nation community approval for every community in BC would be required to obtain First Nations identifiers for BC birth records. As this was unfeasible, our research combined all births (First Nations and non-First Nations) without evaluating First Nations specific risks as they related to the social and physical environment. It has been shown that after controlling for SES and other maternal risk factors, Aboriginal identity is not an independent risk factor for some adverse birth outcomes or differences in risk between First Nation and non-First Nation birth were greatly attenuated [7-9]. Our methods will allow for a higher level of comprehensive analysis, once protocols for research in BC are established by the FNHA.

4.0 Overall Implications and Future Considerations

Reproductive health and pregnancy outcomes are important health measures to study for several reasons, the most important being that exposures and stressors in utero and

early childhood can influence one's entire life trajectory [10-13]. The fetal origins of disease, or "Baker Hypothesis", postulates that perturbation of the early nutritional environment has long-term structural, physiological and neurological impacts on newborns that predispose them to chronic diseases in adulthood including type 2 diabetes, hypertension, coronary heart disease and obesity [11,12]. This hypothesis has been expanded to include excess fetal glucocorticoid exposure from maternal social stressors acting on the HPA-axis and potentially leading to early life programming of disease [14,15]. These early developmental exposures may elicit epigenomic modifications and dysregulation such as DNA methylation that have lifelong and potentially transgenerational implications for health [16–18].

Similarly, it is now well demonstrated that SES-related risk factors can also have a life-course trajectory latency period on health [19–22] which can lead to the intergenerational transmission of poverty and poor health [23]. This is particularly relevant for Indigenous populations in North America and elsewhere who have endured centuries of colonization and on-going systemic and institutionally entrenched violence, racism and marginalization. The effect of this type of enduring trauma goes beyond the lifespan of individuals to persist inter-generationally within families and whole communities [24–28]. Therefore, the inequities of health among newborns as a result of different social and geographic sub-populations represent an intolerable but incessant cycle of injustice.

In Canada, roughly 6% of births are considered LBW which corresponds to approximately 25,000 affected infants each year [29]. It is estimated that between two and ten percent of these can be directly attributable to environmental exposures excluding tobacco, alcohol and illicit drug use amounting to roughly $1.5 million in direct and indirect costs each year [30]. However, this figure does not capture the latent and long-term costs associated with LBW that disproportionately affect low SES households [31-33].

The assessment of the long-term effects of being born small is difficult to discern due to the confounding of other SES-related risk factors. A 26 year follow-up study of the 1970 British Birth Cohort found that children born full-term but SGA below the 5th percentile demonstrated small but significant deficits in academic achievements at follow-up ages of 5, 10 and 16 [34]. These small differences in school performance may have led to being less likely to have professional or managerial jobs and lower weekly income at age 26. There was also a significant height differential between SGA and average birth weight participants. However, and perhaps just as importantly, there were no reported differences in total years

of education, employment, hours of work per week, marital status, or satisfaction with life. These results remained significant even after adjusting for social class, sex, region of birth, and the presence of fetal or neonatal distress [34].

In other studies of shorter follow-up times, moderate and early preterm birth (< 30 weeks gestation) and lower birth weights were shown to negatively affect school performance after controlling for parental education, and remained when comparing sibling pairs [35]. However, similar results of lower physical size, cognitive scores and academic achievement at age 8 were only found for those SGA infants with impaired post-natal growth (i.e. SGA + failure to thrive) while SGA infants with adequate postnatal growth showed no difference compared to normal growth children [36]. Furthermore, while low and very low birth weight were negatively associated with academic performance, the growth restricted children showed greater sensitivity to parenting techniques around learning and showed compensatory academic effects under conditions of sensitive parenting experiences [37]. These studies show that being born small or preterm does not necessarily imply a life sentence of struggle and hardship, but that the home and community environment matters [38–40]. It is now well-established that access and proximity to green-spaces has a positive effect on the risk of adverse pregnancy outcomes, buffering the exposure to traffic-related air pollution and noise, and may therefore be linked to other chronic health outcomes in the general population in addition to pregnant women and their offspring [41-46]. This is an area of increasing importance and mitigation.

Returning to the FIGO policy statement, they make four recommendations: 1) advocate for exposure reduction policies; 2) work to ensure a healthy food system for all; 3) make environmental health part of health care; and 4) champion environmental justice [1]. Researchers, policy makers, health professionals and community organizers need to work together to accomplish these recommendations.

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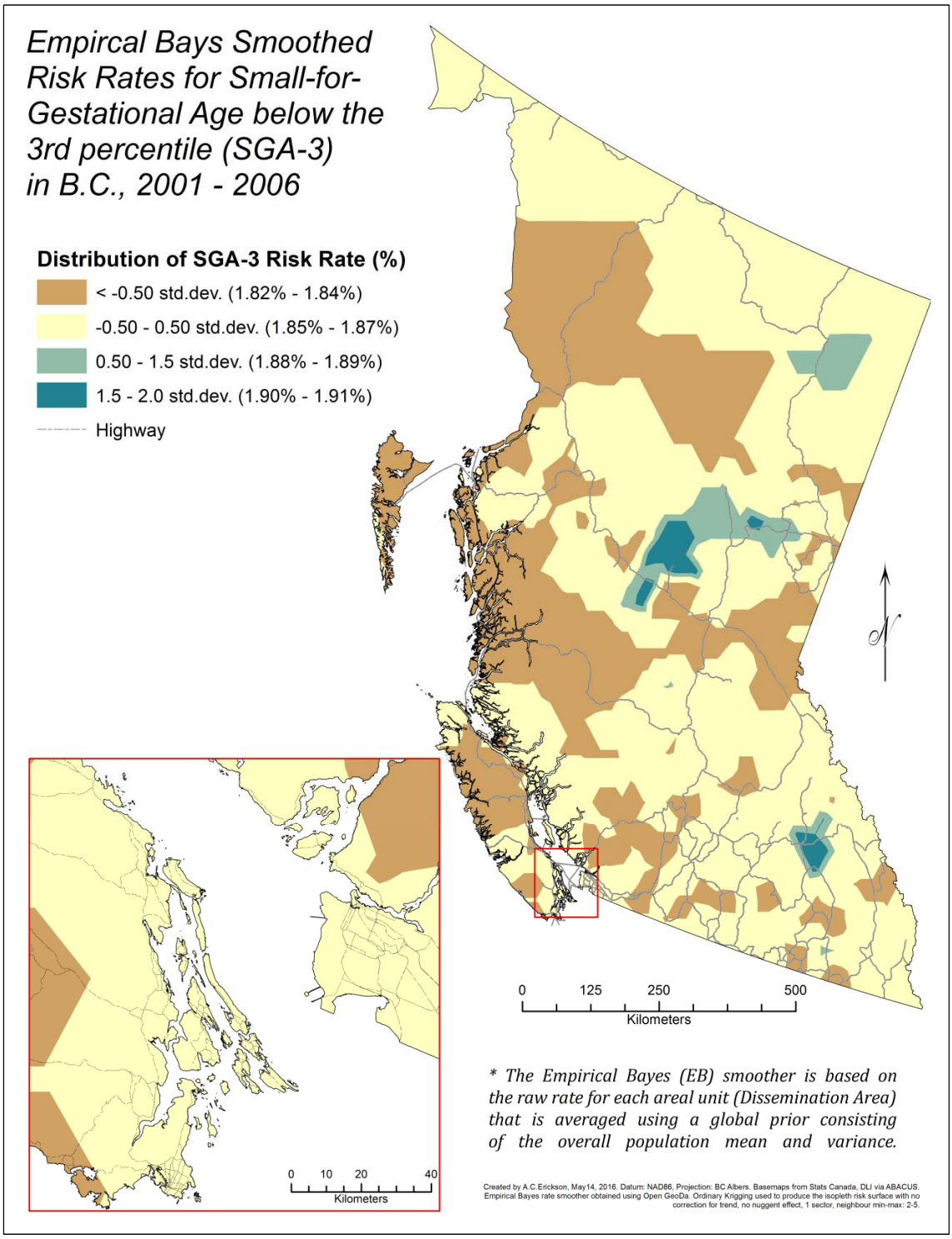
Appendix 1
Risk Surface Maps

Spatial epidemiology is largely concerned with the analysis of spatially continuous disease risk and risk factors. As a result, continuous surface risk maps (or isopleth maps) are desired.

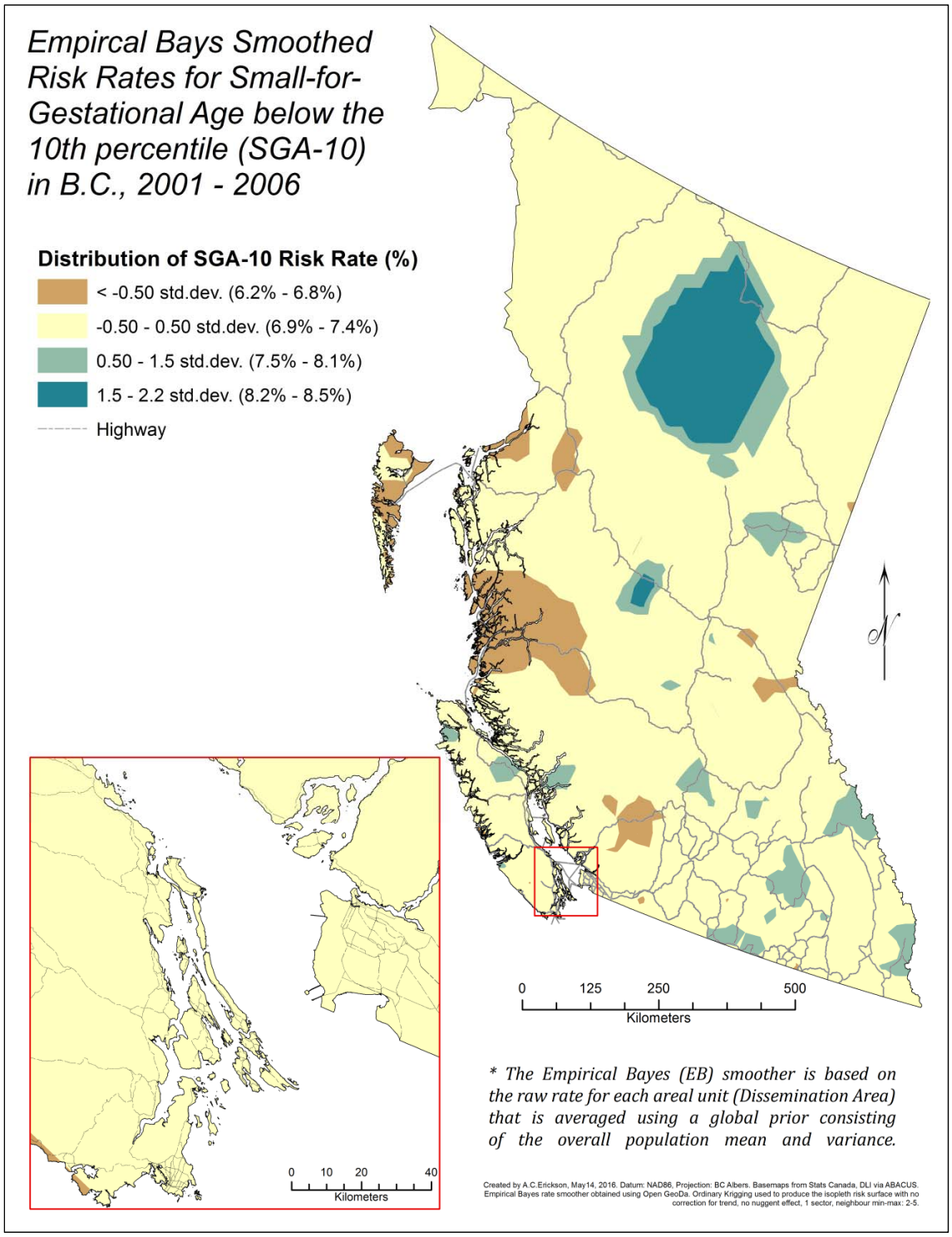
There are several methods available for the spatial interpolation of regional data into a risk surface. For the risk surface maps presented below, I followed the krigging methodology presented by Olaf Berke (*Berke O. 2004. Exploratory disease mapping: kriging the spatial risk function from regional count data. International journal of health geographics. 2004, 3(18)*). Here, two sophisticated methods are combines to create continuous spatial risk maps of adverse pregnancy outcomes. First, empirical Bayes estimation is used to smooth the spatial risk estimates to stabilize the standard errors and reduce the impact of outliers by "borrowing strength from the ensemble" in which unstable variances from small area samples are shrunk to the global variance by pooling information across the study region. The process could be seen as related to internal standardization in epidemiology.

Second, ordinary kriging was used to predict (interpolate) the smoothed rates into a continuous risk surface. In order to remove the potential for over-smoothing that krigging would perform by modeling the small scale spatial variability, the semivariogram was modelled without nugget effect which leads to the direct interpolation at the sampling sites (i.e. the DAs with known rates) and smoothed predictions at the unknown sites shrunk towards the global mean value of the estimated trend surface. The resulting maps are easily interpretable to map users, including other researchers and policy makers.

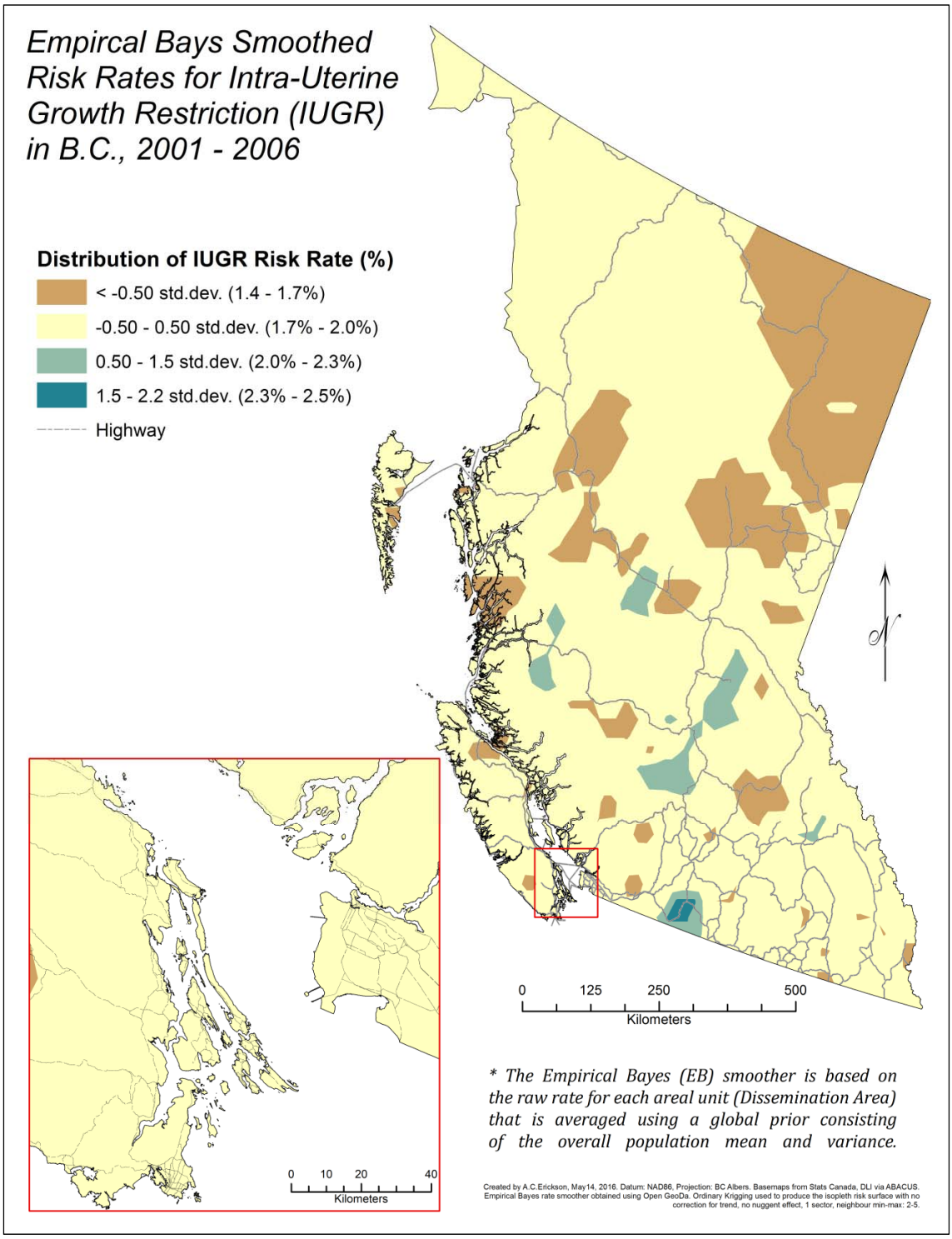
Map 1


Empircal Bays Smoothed Risk Rates for Small-for-Gestational Age below the 3rd percentile (SGA-3) in B.C., 2001 - 2006
Distribution of SGA-3 Risk Rate (%)
< -0.50 std.dev. (1.82% - 1.84%)
-0.50 - 0.50 std.dev. (1.85% - 1.87%)
0.50 - 1.5 std.dev. (1.88% - 1.89%)
1.5 - 2.0 std.dev. (1.90% - 1.91%)
Highway
N
0 125 250 500
Kilometers
0 10 20 40
Kilometers
* The Empirical Bayes (EB) smoother is based on the raw rate for each areal unit (Dissemination Area) that is averaged using a global prior consisting of the overall population mean and variance.
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS.
Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

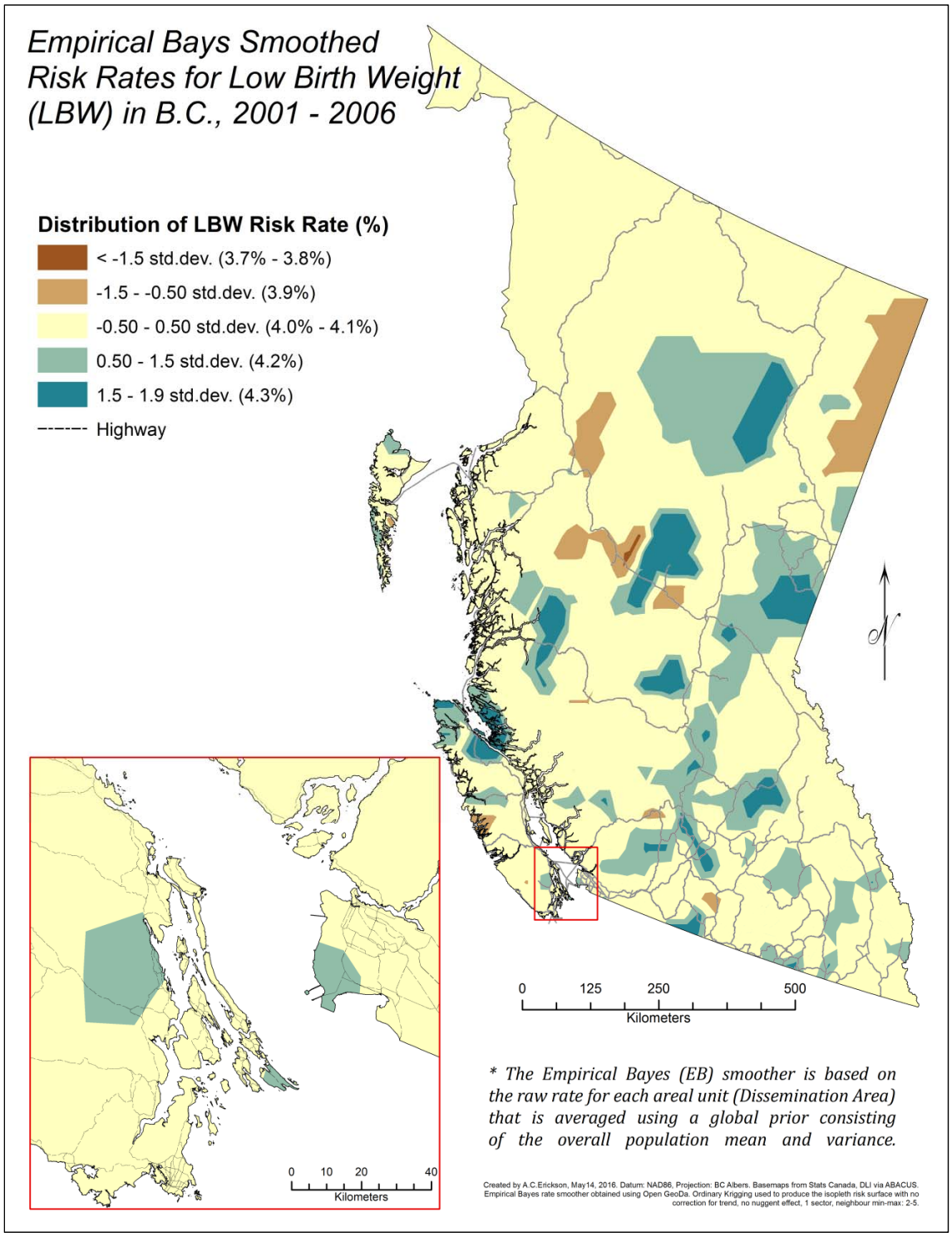
Map 2


Empircal Bays Smoothed Risk Rates for Small-for-Gestational Age below the 10th percentile (SGA-10) in B.C., 2001 - 2006
Distribution of SGA-10 Risk Rate (%)
< -0.50 std.dev. (6.2% - 6.8%)
-0.50 - 0.50 std.dev. (6.9% - 7.4%)
0.50 - 1.5 std.dev. (7.5% - 8.1%)
1.5 - 2.2 std.dev. (8.2% - 8.5%)
Highway
N
0 125 250 500
Kilometers
0 10 20 40
Kilometers
* The Empirical Bayes (EB) smoother is based on the raw rate for each areal unit (Dissemination Area) that is averaged using a global prior consisting of the overall population mean and variance.
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS.
Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

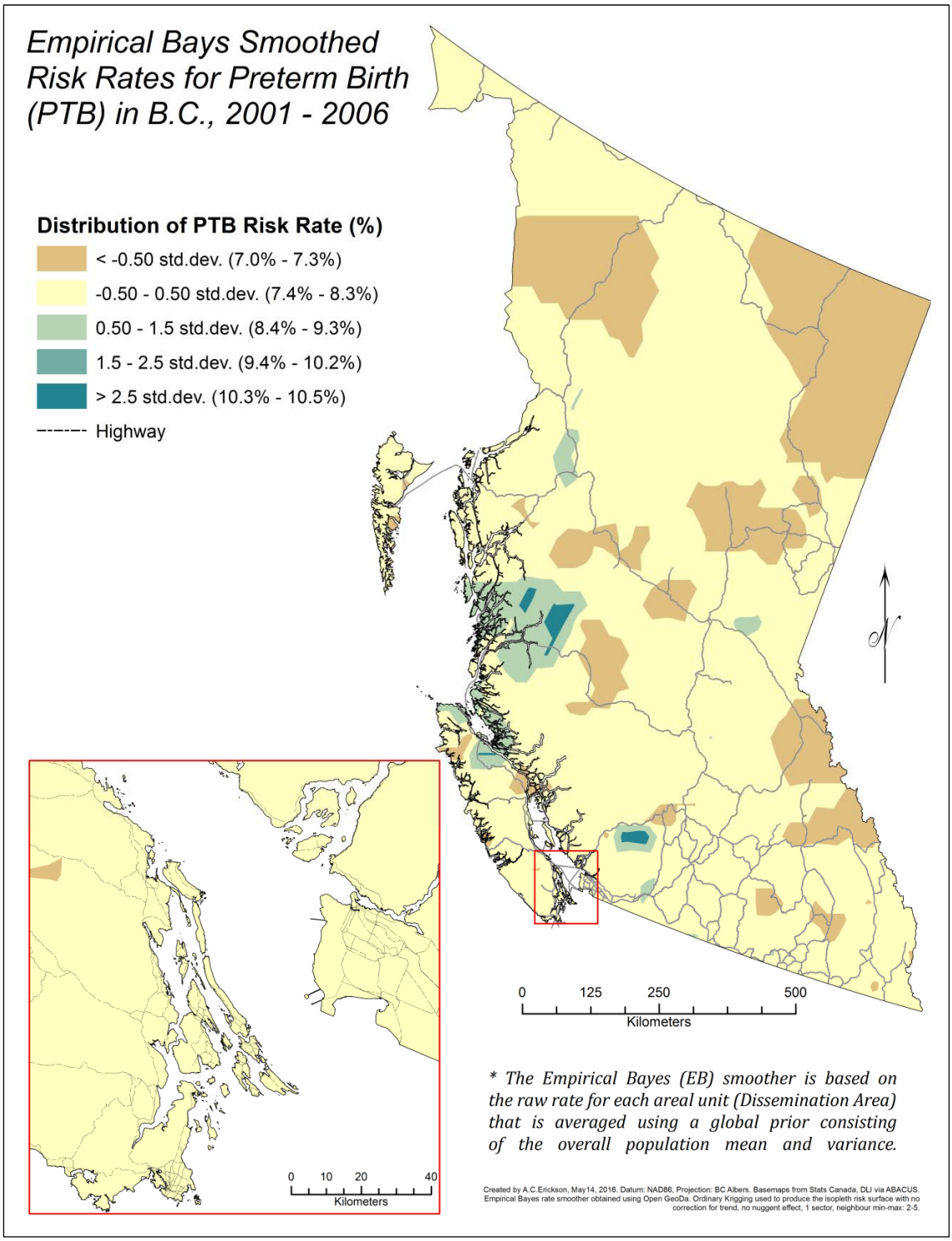
Map 3


Empircal Bays Smoothed Risk Rates for Intra-Uterine Growth Restriction (IUGR) in B.C., 2001 - 2006
Distribution of IUGR Risk Rate (%)
< -0.50 std.dev. (1.4 - 1.7%)
-0.50 - 0.50 std.dev. (1.7% - 2.0%)
0.50 - 1.5 std.dev. (2.0% - 2.3%)
1.5 - 2.2 std.dev. (2.3% - 2.5%)
Highway
N
0 125 250 500
Kilometers
0 10 20 40
Kilometers
* The Empirical Bayes (EB) smoother is based on the raw rate for each areal unit (Dissemination Area) that is averaged using a global prior consisting of the overall population mean and variance.
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS.
Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

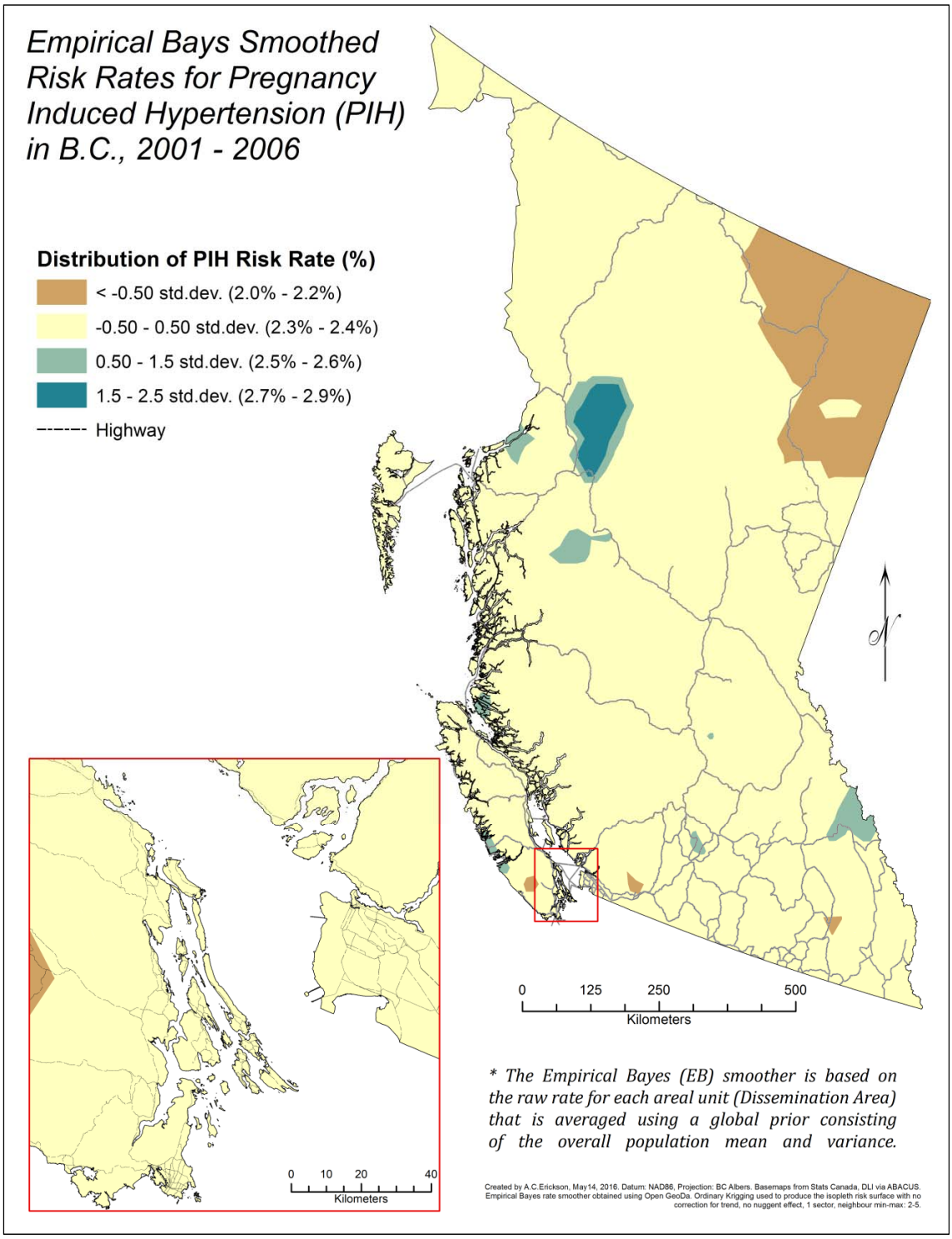
Map 4


Empirical Bays Smoothed Risk Rates for Low Birth Weight (LBW) in B.C., 2001 - 2006
Distribution of LBW Risk Rate (%)
< -1.5 std.dev. (3.7% - 3.8%)
-1.5 - -0.50 std.dev. (3.9%)
-0.50 - 0.50 std.dev. (4.0% - 4.1%)
0.50 - 1.5 std.dev. (4.2%)
1.5 - 1.9 std.dev. (4.3%)
Highway
0 125 250 500
Kilometers
0 10 20 40
Kilometers
* The Empirical Bayes (EB) smoother is based on the raw rate for each areal unit (Dissemination Area) that is averaged using a global prior consisting of the overall population mean and variance.
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS.
Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

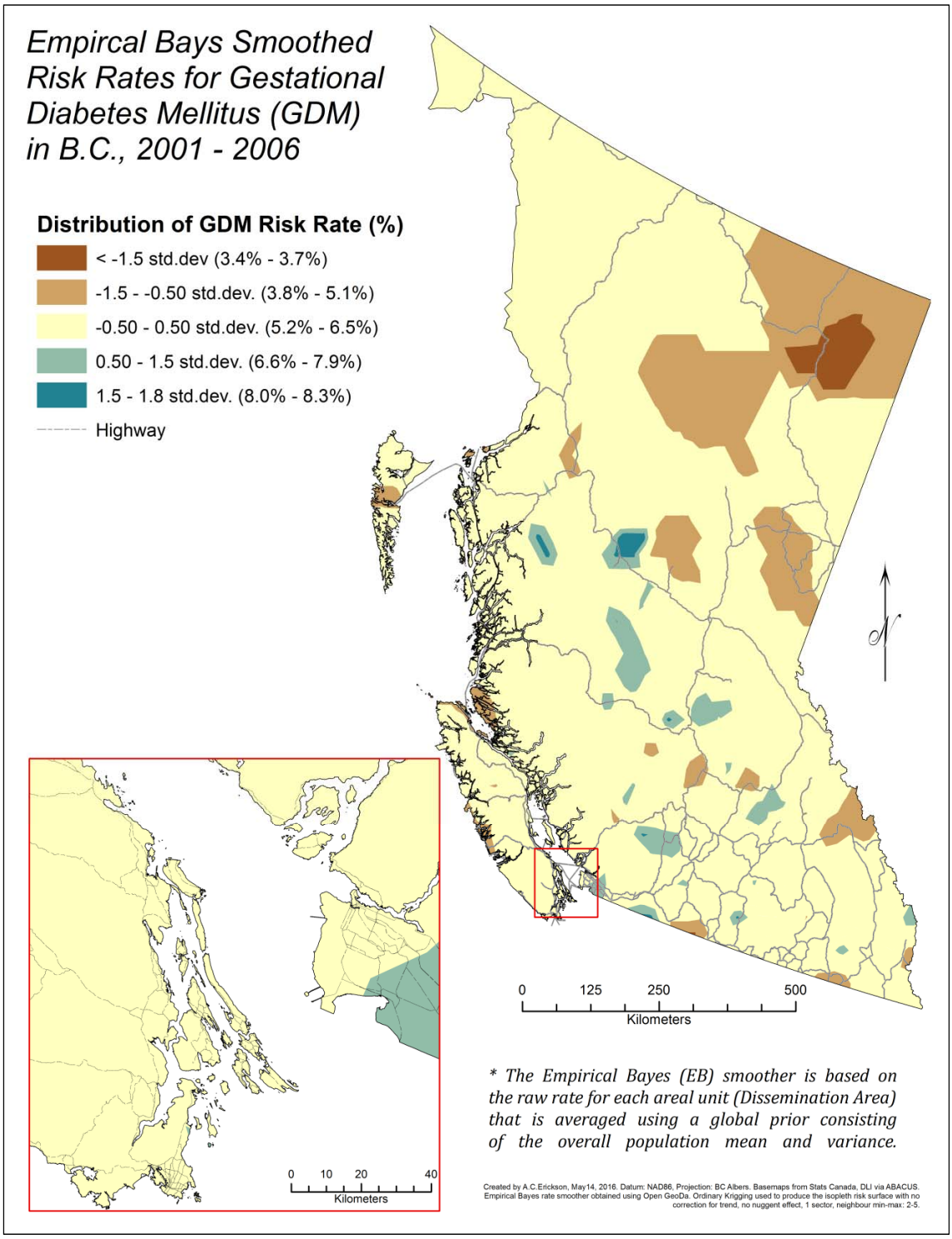
Map 5


Empirical Bays Smoothed Risk Rates for Preterm Birth (PTB) in B.C., 2001 - 2006
Distribution of PTB Risk Rate (%)
< -0.50 std.dev. (7.0% - 7.3%)
-0.50 - 0.50 std.dev. (7.4% - 8.3%)
0.50 - 1.5 std.dev. (8.4% - 9.3%)
1.5 - 2.5 std.dev. (9.4% - 10.2%)
> 2.5 std.dev. (10.3% - 10.5%)
Highway
0 125 250 500
Kilometers
0 10 20 40
Kilometers
* The Empirical Bayes (EB) smoother is based on the raw rate for each areal unit (Dissemination Area) that is averaged using a global prior consisting of the overall population mean and variance.
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS. Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

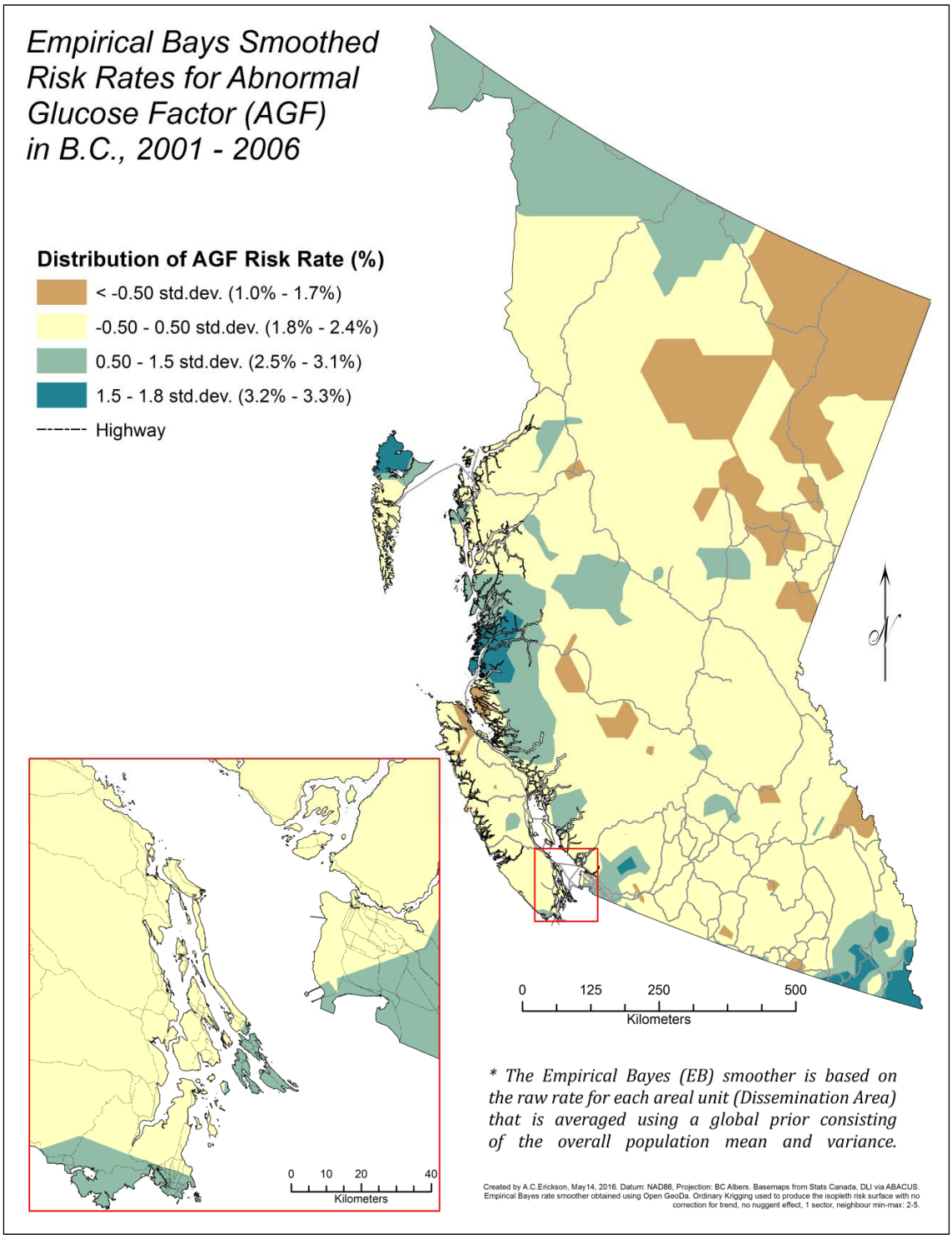
Map 6


Empirical Bays Smoothed Risk Rates for Pregnancy Induced Hypertension (PIH) in B.C., 2001 - 2006
Distribution of PIH Risk Rate (%)
< -0.50 std.dev. (2.0% - 2.2%)
-0.50 - 0.50 std.dev. (2.3% - 2.4%)
0.50 - 1.5 std.dev. (2.5% - 2.6%)
1.5 - 2.5 std.dev. (2.7% - 2.9%)
Highway
N
0 125 250 500
Kilometers
0 10 20 40
Kilometers
* The Empirical Bayes (EB) smoother is based on the raw rate for each areal unit (Dissemination Area) that is averaged using a global prior consisting of the overall population mean and variance.
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS.
Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

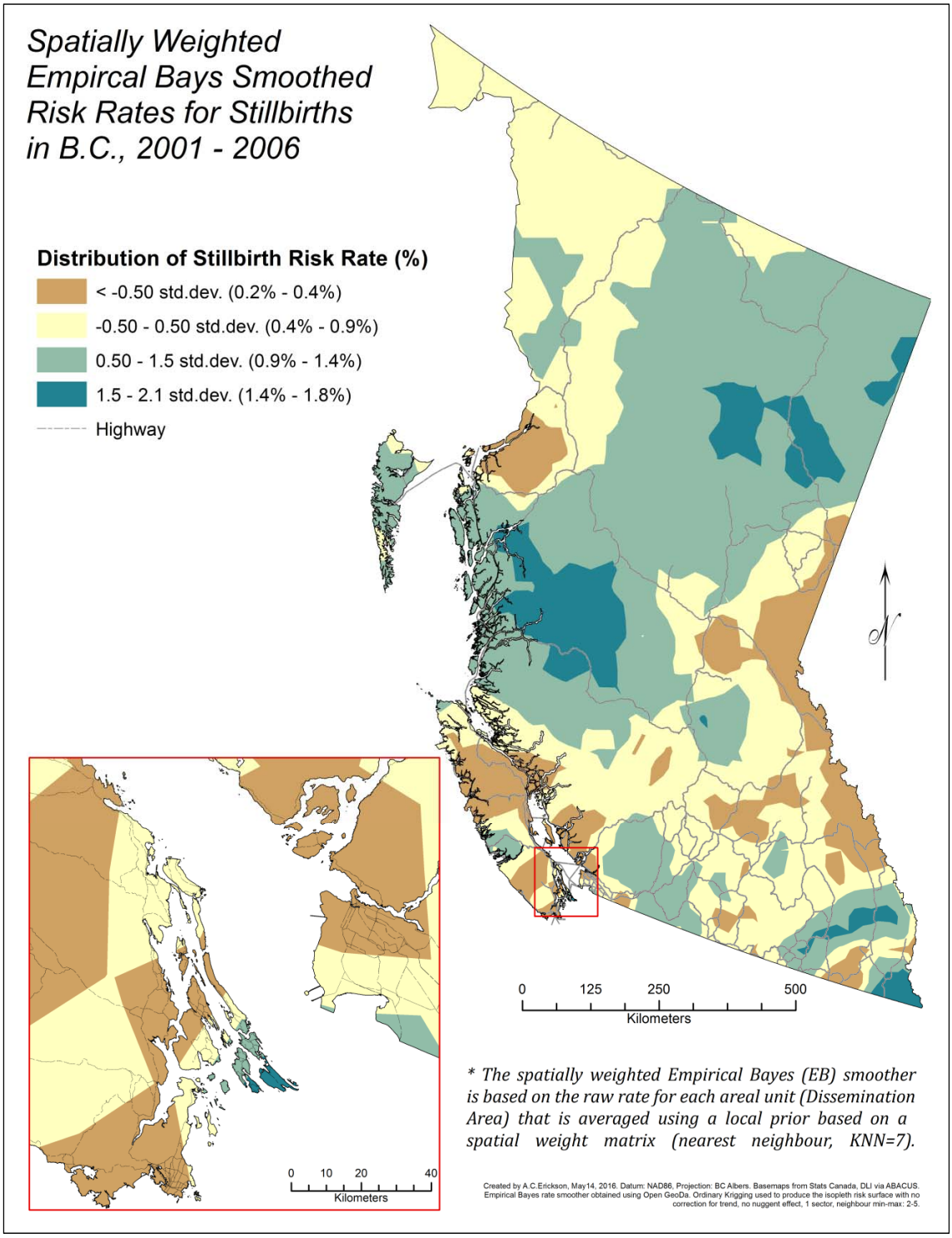
Map 7


Empircal Bays Smoothed Risk Rates for Gestational Diabetes Mellitus (GDM) in B.C., 2001 - 2006
Distribution of GDM Risk Rate (%)
< -1.5 std.dev (3.4% - 3.7%)
-1.5 - -0.50 std.dev. (3.8% - 5.1%)
-0.50 - 0.50 std.dev. (5.2% - 6.5%)
0.50 - 1.5 std.dev. (6.6% - 7.9%)
1.5 - 1.8 std.dev. (8.0% - 8.3%)
Highway
N
0 125 250 500
Kilometers
0 10 20 40
Kilometers
* The Empirical Bayes (EB) smoother is based on the raw rate for each areal unit (Dissemination Area) that is averaged using a global prior consisting of the overall population mean and variance.
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS.
Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

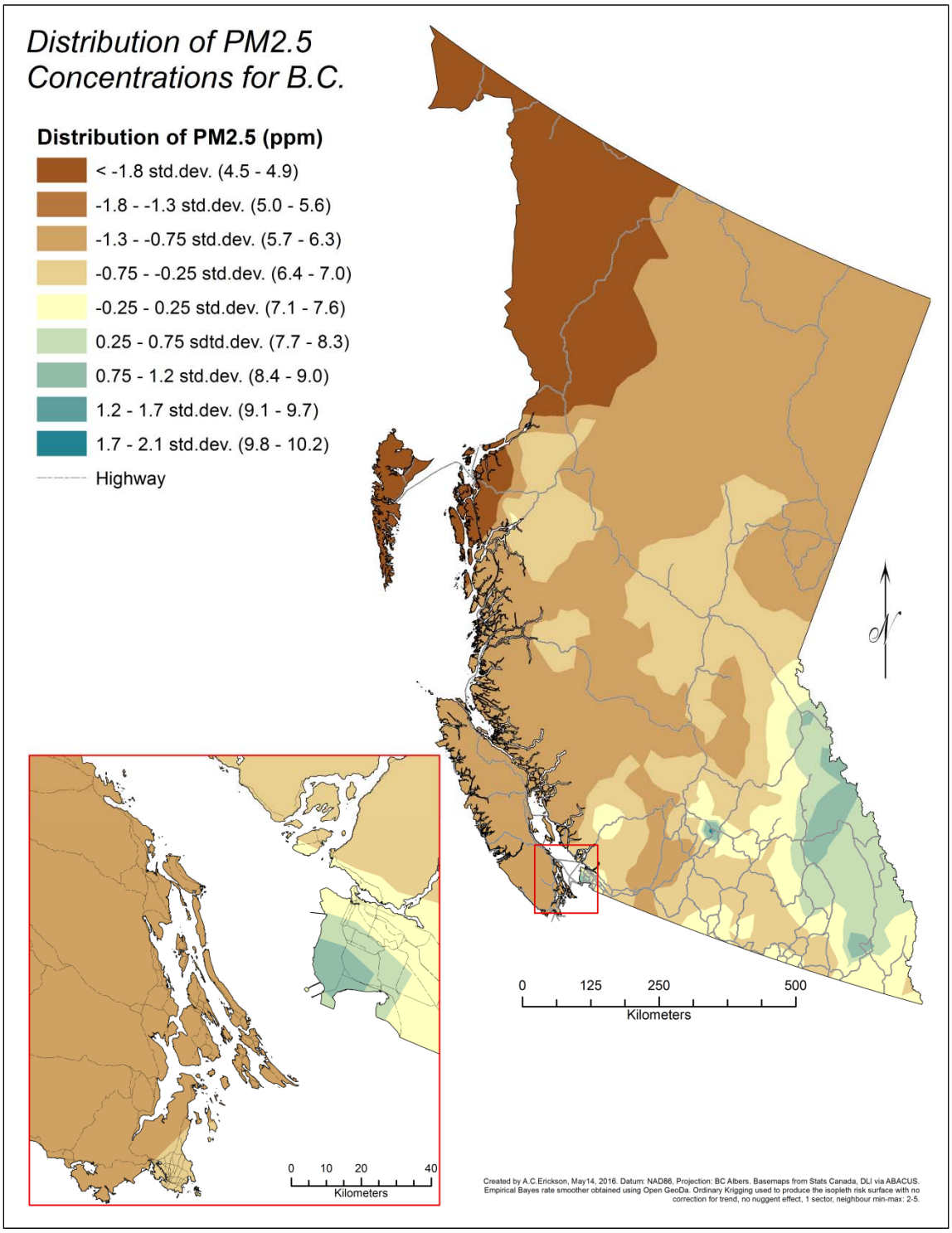
Map 8


Empirical Bays Smoothed Risk Rates for Abnormal Glucose Factor (AGF) in B.C., 2001 - 2006
Distribution of AGF Risk Rate (%)
< -0.50 std.dev. (1.0% - 1.7%)
-0.50 - 0.50 std.dev. (1.8% - 2.4%)
0.50 - 1.5 std.dev. (2.5% - 3.1%)
1.5 - 1.8 std.dev. (3.2% - 3.3%)
Highway
N
0 125 250 500
Kilometers
0 10 20 40
Kilometers
* The Empirical Bayes (EB) smoother is based on the raw rate for each areal unit (Dissemination Area) that is averaged using a global prior consisting of the overall population mean and variance.
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS.
Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

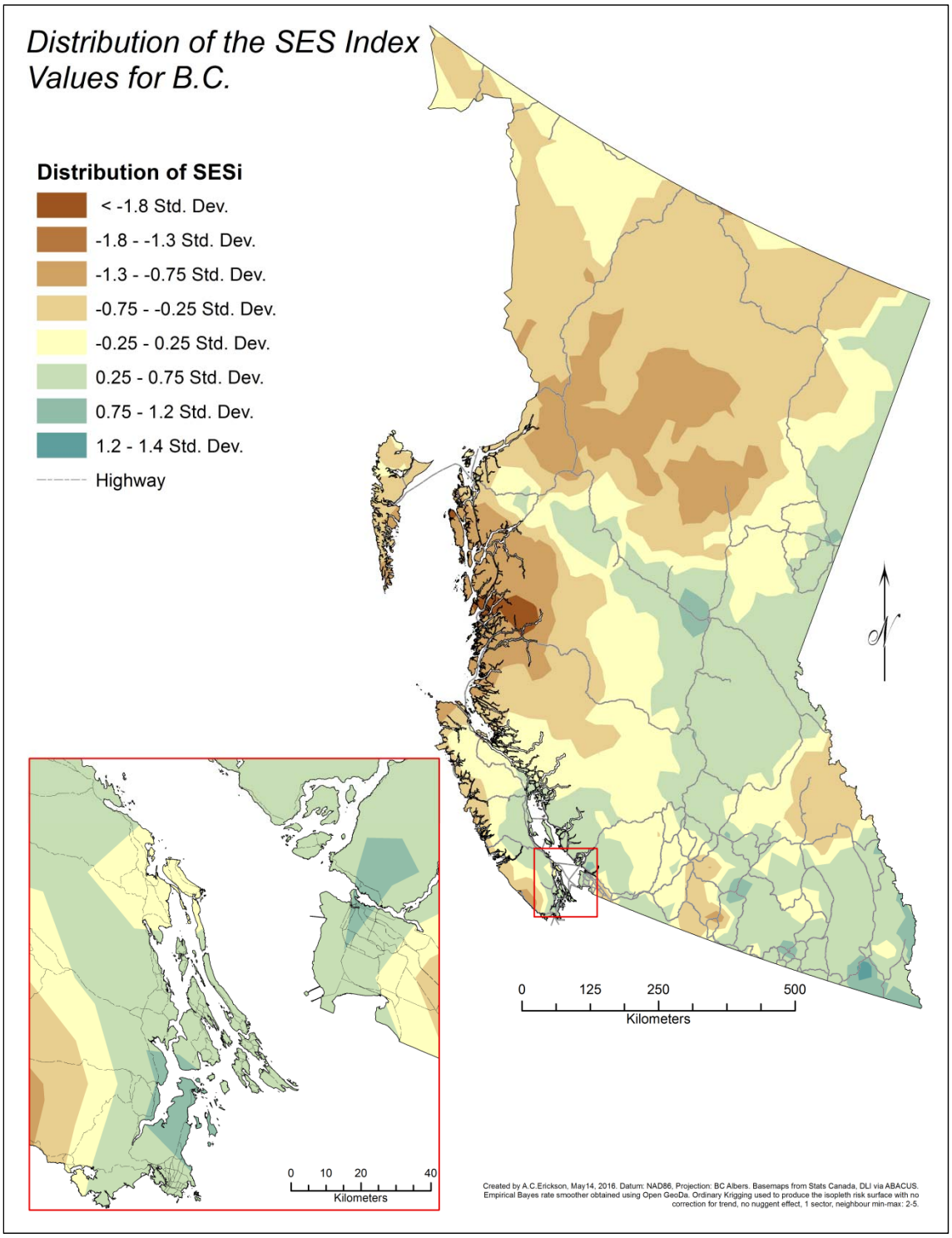
Map 9


Spatially Weighted Empircal Bays Smoothed Risk Rates for Stillbirths in B.C., 2001 - 2006
Distribution of Stillbirth Risk Rate (%)
< -0.50 std.dev. (0.2% - 0.4%)
-0.50 - 0.50 std.dev. (0.4% - 0.9%)
0.50 - 1.5 std.dev. (0.9% - 1.4%)
1.5 - 2.1 std.dev. (1.4% - 1.8%)
Highway
N
0 125 250 500
Kilometers
0 10 20 40
Kilometers
* The spatially weighted Empirical Bayes (EB) smoother is based on the raw rate for each areal unit (Dissemination Area) that is averaged using a local prior based on a spatial weight matrix (nearest neighbour, KNN=7).
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS.
Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

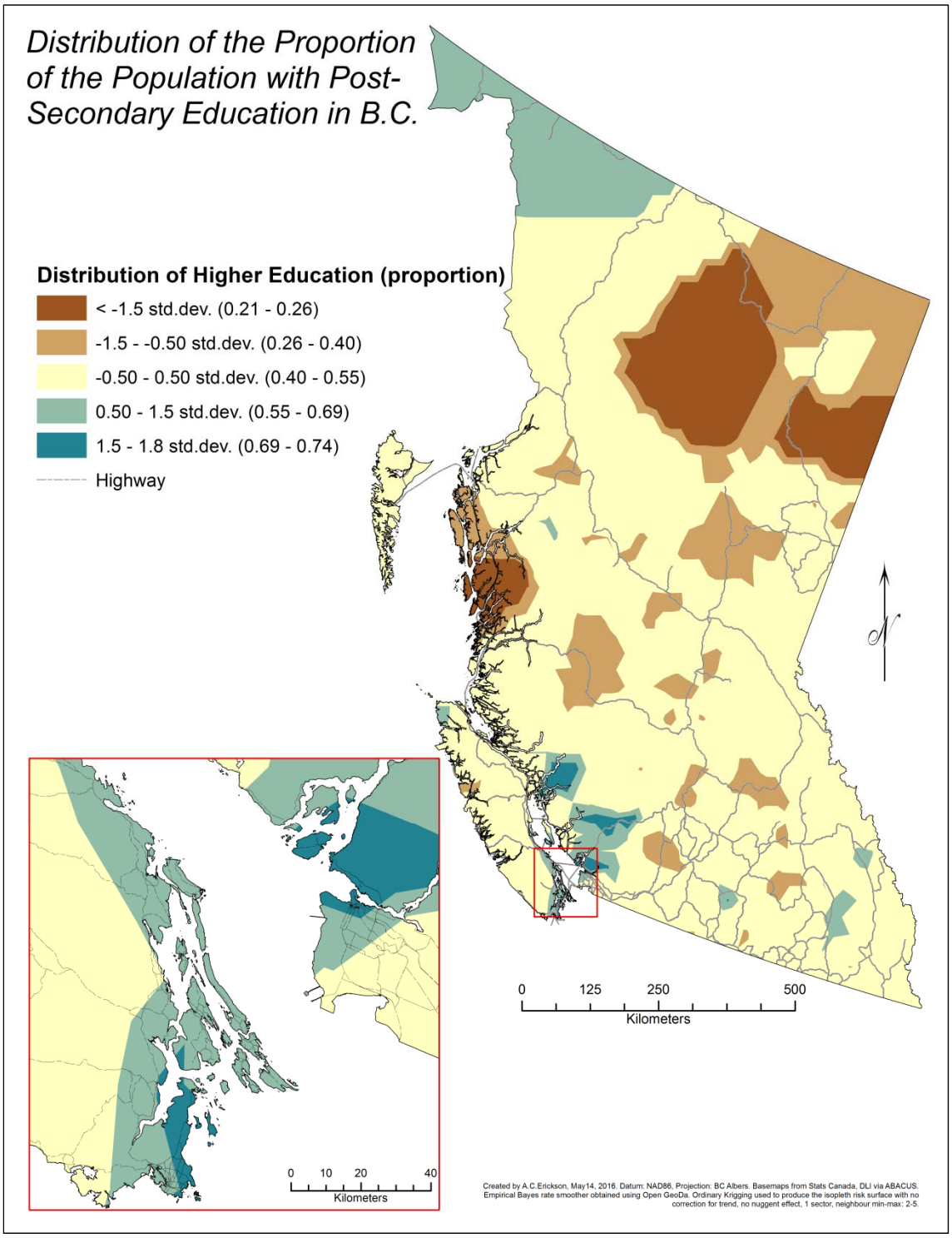
Map 10


Distribution of PM2.5 Concentrations for B.C.
Distribution of PM2.5 (ppm)
< -1.8 std.dev. (4.5 - 4.9)
-1.8 - -1.3 std.dev. (5.0 - 5.6)
-1.3 - -0.75 std.dev. (5.7 - 6.3)
-0.75 - -0.25 std.dev. (6.4 - 7.0)
-0.25 - 0.25 std.dev. (7.1 - 7.6)
0.25 - 0.75 sdtd.dev. (7.7 - 8.3)
0.75 - 1.2 std.dev. (8.4 - 9.0)
1.2 - 1.7 std.dev. (9.1 - 9.7)
1.7 - 2.1 std.dev. (9.8 - 10.2)
Highway
N
0 125 250 500
Kilometers
0 10 20 40
Kilometers
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS.
Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

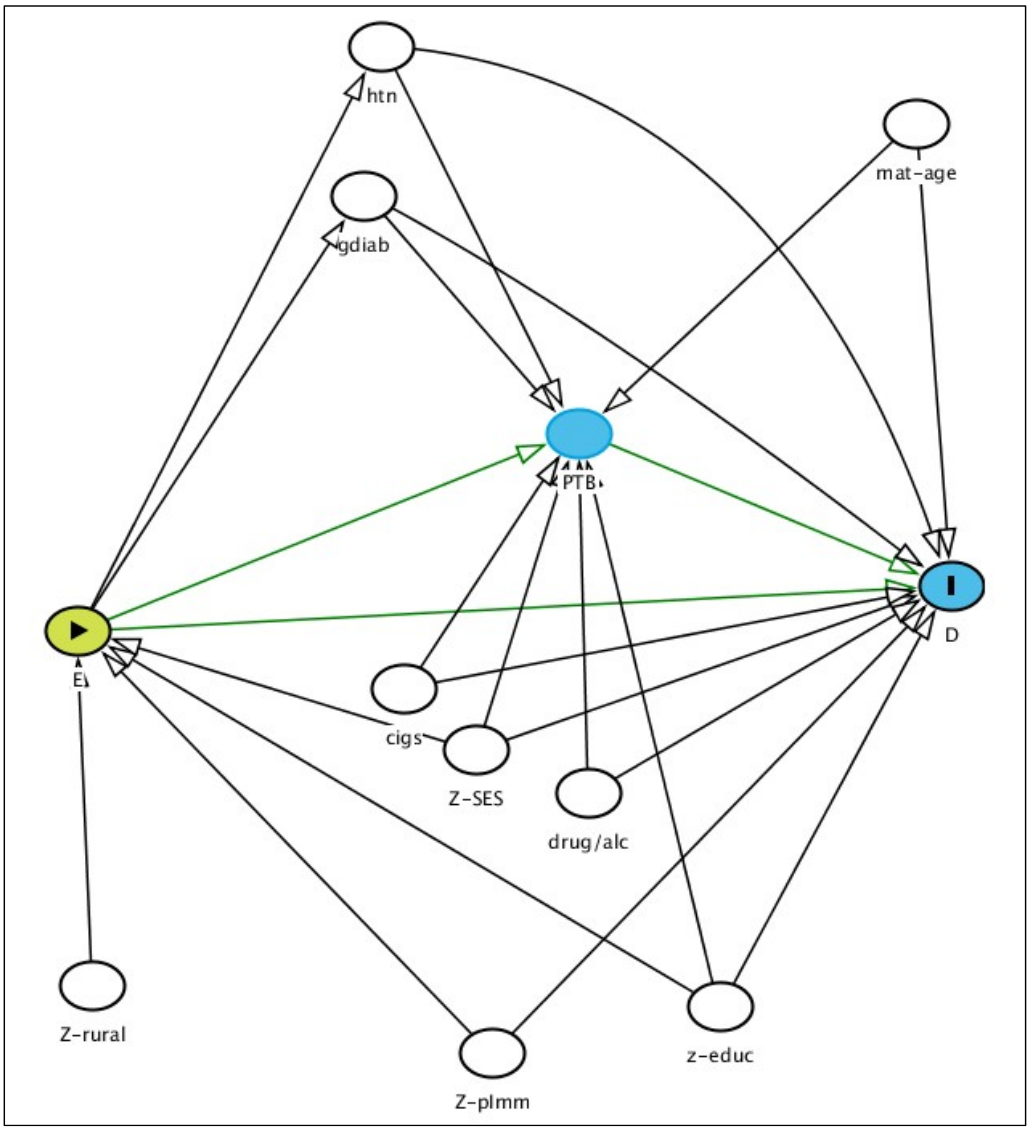
Map 11


Distribution of the SES Index Values for B.C.
Distribution of SESi
< -1.8 Std. Dev.
-1.8 - -1.3 Std. Dev.
-1.3 - -0.75 Std. Dev.
-0.75 - -0.25 Std. Dev.
-0.25 - 0.25 Std. Dev.
0.25 - 0.75 Std. Dev.
0.75 - 1.2 Std. Dev.
1.2 - 1.4 Std. Dev.
Highway
N
0 125 250 500
Kilometers
0 10 20 40
Kilometers
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS.
Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

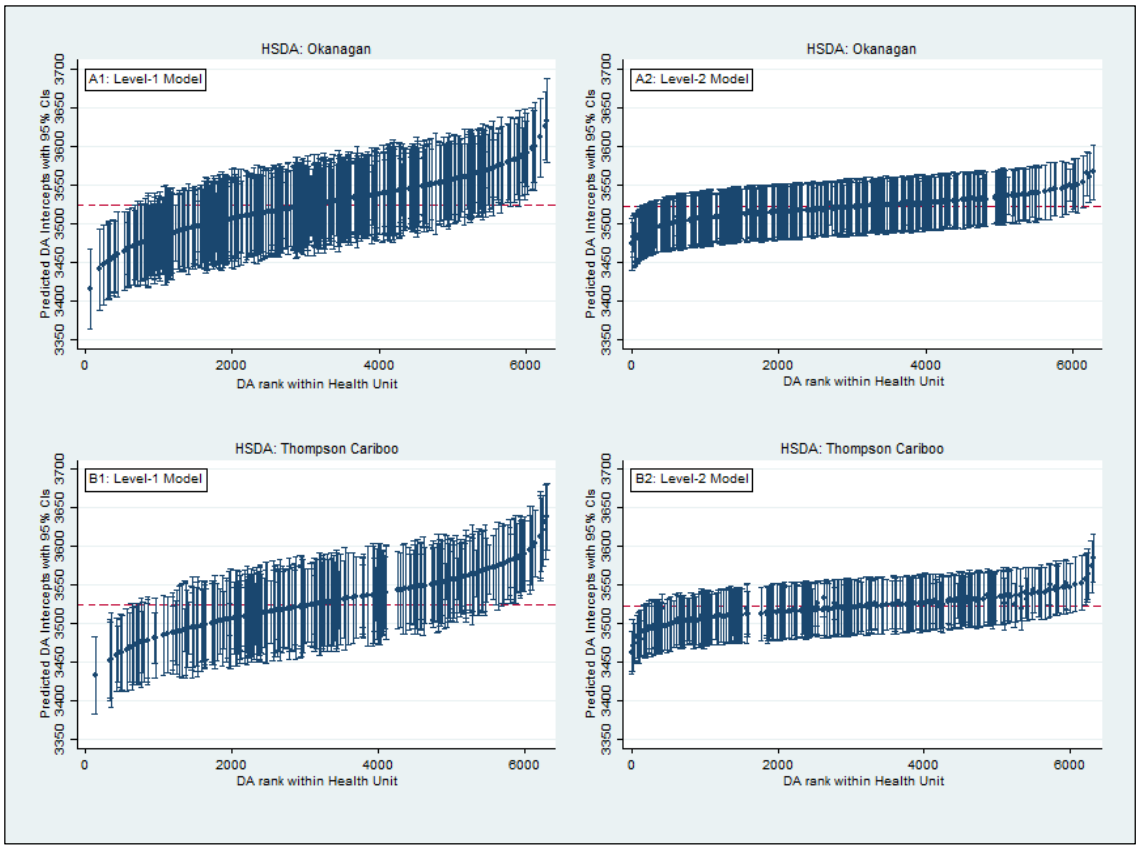
Map 12


Distribution of the Proportion of the Population with Post-Secondary Education in B.C.
Distribution of Higher Education (proportion)
< -1.5 std.dev. (0.21 - 0.26)
-1.5 - -0.50 std.dev. (0.26 - 0.40)
-0.50 - 0.50 std.dev. (0.40 - 0.55)
0.50 - 1.5 std.dev. (0.55 - 0.69)
1.5 - 1.8 std.dev. (0.69 - 0.74)
Highway
N
0 125 250 500
Kilometers
0 10 20 40
Kilometers
Created by A.C.Erickson, May14, 2016. Datum: NAD86, Projection: BC Albers. Basemaps from Stats Canada, DLI via ABACUS.
Empirical Bayes rate smoother obtained using Open GeoDa. Ordinary Krigging used to produce the isopleth risk surface with no correction for trend, no nuggent effect, 1 sector, neighbour min-max: 2-5.

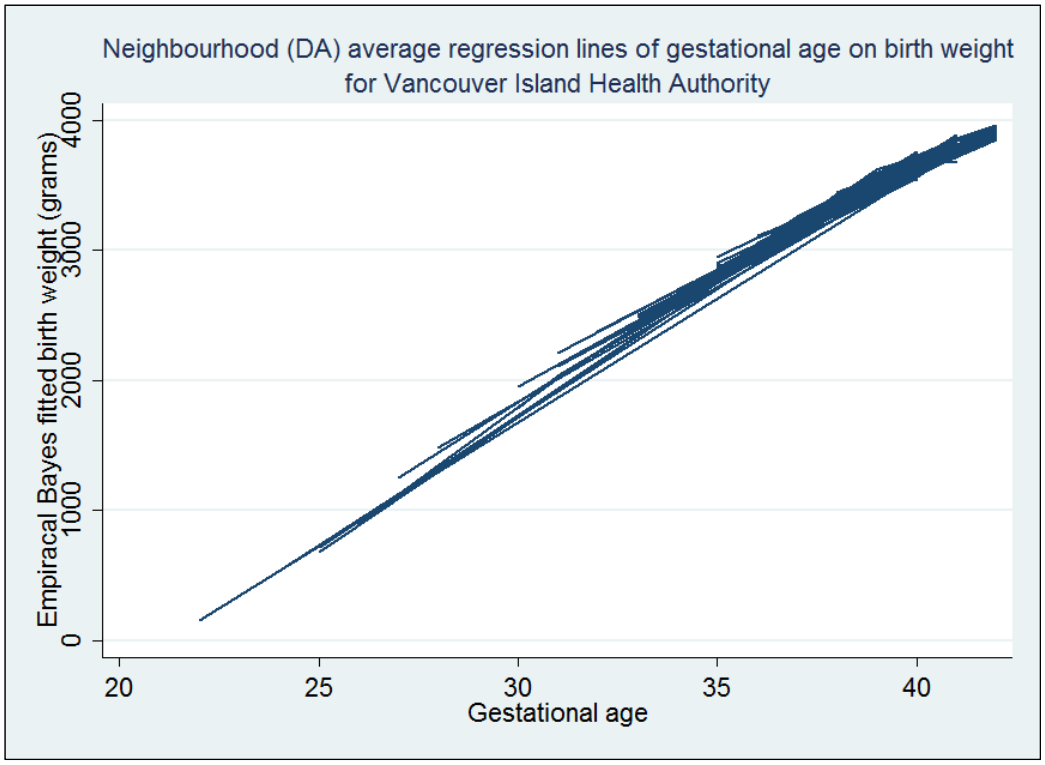
Appendix 2
Additional Figures for Chapter 4



Directional Acyclic Graphic of hypothesized causal process, where E: $PM_{2.5}$ exposure, D: birth weight, PTB: preterm birth, gdiab: gestational diabetes, htn: gestational hypertension, Z: level-2 or neighbourhood-level variables



Caterpillar plot of the DA-level random intercepts comparing the Level-1 model with only individual-level variables (A1 & B1) to the Level-2 model containing DA-level variables (A2 & B2) for two different Health Service Delivery Areas. The Level-2 models explain a substantial proportion of the between-DA random intercept variance in birth weight



Example of the variability between the random slopes for gestational age on birth weight for the neighbourhood DAs within a given regional health authority (Vancouver Island)

Appendix 3
Results for SGA-3, SGA-10, IUGR, Term LBW, and PTB

BC specific birth weight reference charts [1] were used to identify births that were small-for-gestational age below the 3rd and 10th percentile for weight and sex (SGA-3 and SGA-10 respectively). After exclusions, there were 230,903 singleton liveborn births located in 6,338 neighbourhood DAs (min. = 1, max. = 779, avg. = 36). Excluded observations included: missing birth weight (n = 46), missing gestational age (n = 373), stillbirths (n = 1,047), missing cigarettes/day (n = 2,484), missing $PM_{2.5}$ (n = 1,502), missing sex (n = 5). Sensitivity analyses were run including stillbirths as well as using a Canadian-wide birth weight reference to classify SGA-3 and SGA-10 [2] with only very minor differences for some coefficients and standard errors.

Term low birth weight (tLBW) is defined as birth which reached a gestational age of 37 completed weeks but had birth weights less than 2,500 grams. There were 214,178 singleton (liveborn and stillborn) births located in 6,337 neighbourhood DAs (min. = 1, max. = 709, avg. = 34). Excluded observations included: births with a missing or listed gestational age <37 weeks (18,547), missing birth weight (n = 46), missing cigarettes/day (n = 2,204), missing $PM_{2.5}$ (n = 1,381), missing sex (n = 4).

Intrauterine growth restriction (IUGR) is a pre-defined BCPDR field derived from birth charts as being physician identified IUGR during the antenatal period using ultrasound imaging growth parameters. After exclusions, there were 231,305 singletons liveborn births located in 6,338 neighbourhood DAs (min. = 1, max. = 780, avg. = 37). Excluded observations included: stillbirths (1,052), missing cigarettes/day (n = 2,493), missing $PM_{2.5}$ (n = 1,502), missing sex (n = 5). A sensitivity analysis including stillbirths was not able to be performed; however, results are not expected to differ much given the outcome of similar previous analyses.

Both regular (maximum likelihood) logistic regression with robust standard errors as well as random intercept logistic regression were used to calculate and compared results. While both types of statistical techniques account for the within DA clustering of the individual observations, the desire to quantify the variability for the between-DA intercept was the reason for using the random intercept methods. Comparison of the coefficients and standard errors between similar model specifications saw only very slight differences in some of the standard errors while most of the coefficients were nearly identical for all

outcomes and models tested. All the figures below therefore use the results from the regular logistic regressions.

Figure 1 shows the odds ratios with 95% confidence intervals (OR, 95% CI) for the individual and DA-level variables. All four birth weight outcomes show similar trends for most of the variables. The two exceptions for the individual (level-1) variables include type II diabetes mellitus (T2-diabetes) and gestational diabetes (Gest. Diabetes), demonstrating protective associations for SGA-3 and SGA-10. The reason for this is unclear. With respect to the DA (level-2) variables, only rural residence stands out for IUGR as demonstrating a protective association. This could be a data registry related issue given that IUGR is the only outcome of the four which is an independent BCPDR data field and for which data completeness for rural health centres can be sub-optimal (personal communication with BCPDR staff).

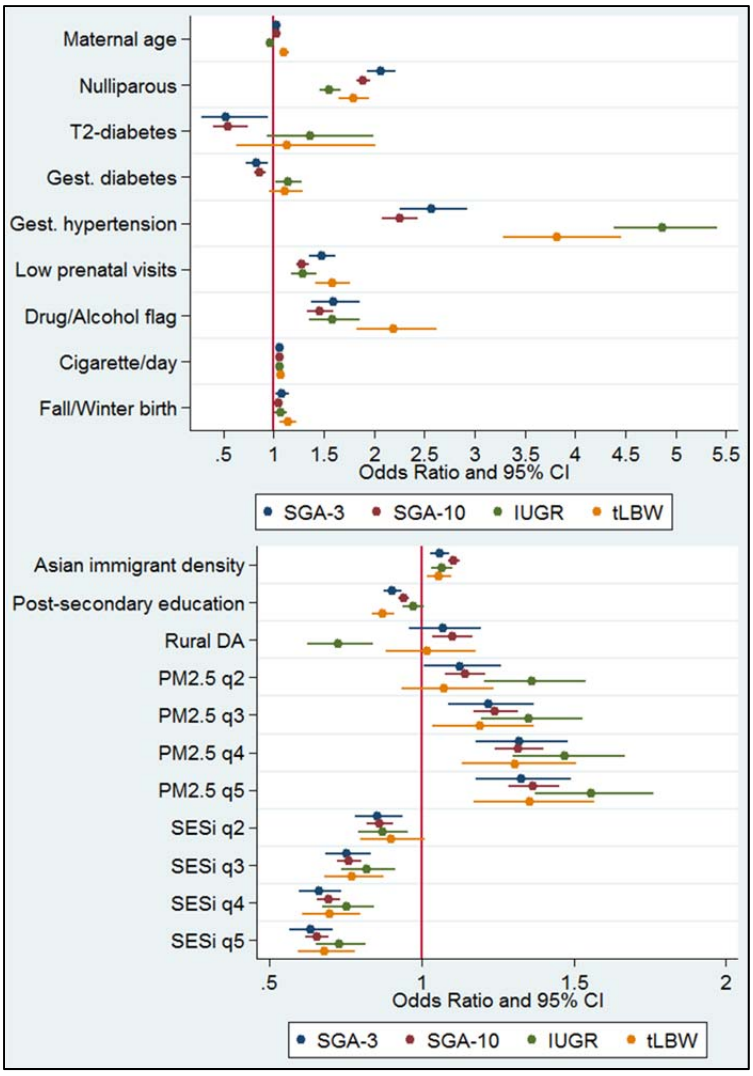


Figure 1: Adjusted odds ratios and 95% confidence intervals (95% CI) individual and neighbourhood-level variables on measures of adverse fetal growth

The observed ORs in Figure 1 for all four outcomes confirm our findings in Chapter 4 regarding the negtive association of $PM_{2.5}$ on birth weight and fetal growth. Figure 1 shows a consistent dose-effect for all four measure of adverse fetal growth. These results also further confirm the findings of SES, higher proportions of neighbourhood-level post-secondary education and the trends observed for neighbourhoods with higher densities of Asian immigrant populations. The increased ORs for the Asian immigran density variable is likely not due to an inherent pathological mechanism or a proxie for an unmeasured exposure, but likely due to the constitutional differences in birth size [3,4].

SGA-3 & SGA-10

Table 1 shows the results for SGA-3 and SGA-10 from an interaction model between $PM_{2.5}$, SES and urban-rural residence. The predicted probabilities derived from these models are presented in Figure 2 using two different variable perspectives. What these models show is that rising $PM_{2.5}$ always increases the risk of SGA, and that this risk is modestly tempered by rising SES, but only in urban areas. The median odds ratio (MOR) translate the area-level variance to the OR scale which permits the direct comparison of its magnitude to that of the level-1 and level-2 factors [5,6]. The MOR for SGA-3 and SGA-10 signify that, in the median case, a randomly selected individual moving from a low risk DA to a higher risk DA will realize a 38% and 13% increased risk of SGA-3 and SGA-10 respectively. Thus, after adjusting for individual and neighbourhood-level known risk factors, a person's residential neighbourhood still exhibits a greater relevance to their risk of SGA than many of the measured model variables.

Non-linear specifications of $PM_{2.5}$ conditional on SES and urban-rural residence were tested using a quatradic expression of the continuous $PM_{2.5}$ variable as well as its quintile transformation. The former did not show to be significant for SGA-3, and just borderline non-significant for SGA-10 ($p = 0.07$). The quinile transformation of $PM_{2.5}$ showed some indication of non-linearity conditional on SES and urban-rural residence (Table 2 and Figure 3). For urban areas only, there was clear modification of the $PM_{2.5}$ association by SES on the risk of SGA-3 and SGA-10. For rural areas, there was a consistent increase in risk of SGA-3 and SGA-10 with rising $PM_{2.5}$ levels, but showed no statistically significant distinction across the levels of SES. These results are consisent with the findings presented in the endnote for Chapter 4, demonstrating that the mechanisms that operate

through neighbourhood low SES to affect fetal growth are more strongly experienced within urban areas where the relative disparities are more pronounced [7].

Table 1: ORs (95% CI) for SGA-3 and SGA-10 in relation to $PM_{2.5}$, SES, and Rural Residence

	SGA-3-m1 SES*Rural*$PM_{2.5}$ OR (95%CI)	**SGA-10-m1 SES*Rural*$PM_{2.5}$ OR (95%CI)**	**tLBW-m1 SES*Rural*$PM_{2.5}$ OR (95%CI)**
$PM_{2.5}$	1.10 (1.06 – 1.15)	1.11 (1.09 – 1.14)	1.11 (1.06 – 1.17)
SESi	0.83 (0.80 – 0.86)	0.85 (0.83 – 0.87)	0.84 (0.80 – 0.88)
Rural Residence	1.06 (0.92 – 1.23)	1.10 (1.02 – 1.19)	1.02 (0.85 – 1.22)
Asian Immigrant Density	1.07 (1.04 – 1.10)	1.12 (1.10 – 1.14)	1.07 (1.03 – 1.12)
Post-Secondary Education	0.92 (0.89 – 0.95)	0.95 (0.94 – 0.97)	0.89 (0.85 – 0.92)
SESi*$PM_{2.5}$	0.99 (0.96 – 1.02)	1.00 (0.98 – 1.02)	0.98 (0.94 – 1.02)
Rural*SESi	1.29 (1.09 – 1.52)	1.11 (1.02 – 1.21)	1.44 (1.16 – 1.79)
Rural* $PM_{2.5}$	1.12 (1.00 – 1.26)	1.05 (0.99 – 1.12)	1.22 (1.06 – 1.41)
Multilevel Model Outputs			
Intercept	0.011	0.047	0.007
Random intercept Variance	0.036	0.017	0.022
Median OR (95% CI)	1.20 (1.11 – 1.38)	1.13 (1.09 – 1.20)	1.15 (1.04 – 1.76)

Logistic random intercept models adjusted for: maternal age, nulliparous, drug or alcohol flag, maternal smoking; season of birth, First Nation on-reserve birth.

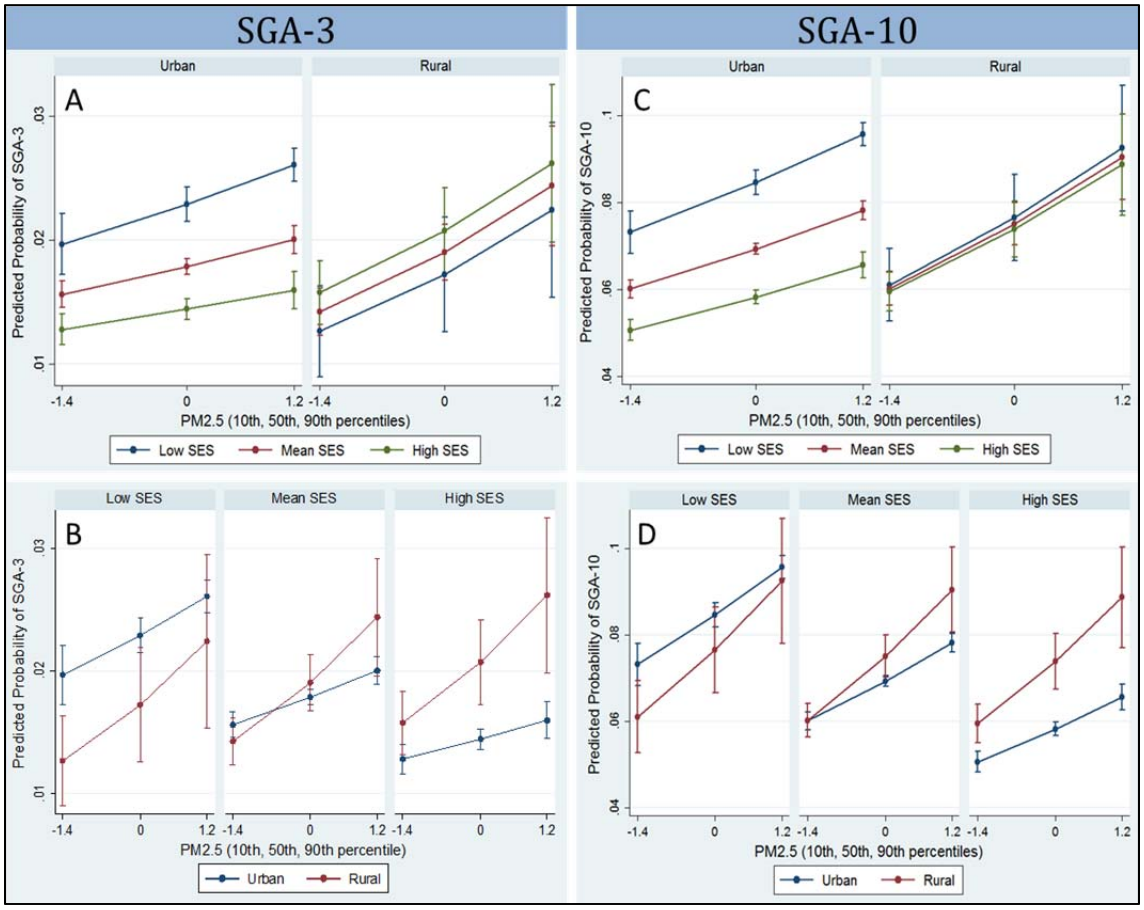


Figure 2: Two different perspectives of the same model

Plot A and B show the predicted probabilities with 95% CIs from SGA-3 model-1 (SGA-3-m1). Plot C and D show the predicted probabilities with 95% CIs from SGA-10 model-1 (SGA-10-m1).

Table 2: ORs (95% CI) for SGA-3, SGA-10, and tLBW in relation to $PM_{2.5}$, SES, and Rural Residence

	SGA-3-m2 SES*Rural*$PM_{2.5}$ OR (95%CI)	SGA-10-m2 SES*Rural*$PM_{2.5}$ OR (95%CI)	tLBW-m2 SES*Rural*$PM_{2.5}$ OR (95%CI)
$PM_{2.5}$ quintile			
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	1.17 (1.01 – 1.35)	1.16 (1.07 – 1.25)	1.07 (0.90 – 1.28)
Q3	1.27 (1.11 – 1.46)	1.26 (1.18 – 1.36)	1.22 (1.03 – 1.45)
Q4	1.34 (1.17 – 1.54)	1.36 (1.26 – 1.46)	1.27 (1.08 – 1.52)
Q5	1.41 (1.22 – 1.64)	1.42 (1.32 – 1.53)	1.50 (1.26 – 1.77)
SESi	0.93 (0.83 – 1.04)	0.92 (0.87 – 0.98)	1.00 (0.87 – 1.15)
Rural Residence	0.94 (0.78 – 1.13)	1.03 (0.94 – 1.14)	0.73 (0.57 – 0.93)
Rural*$PM_{2.5}$ quintile			
Rural*Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Rural*Q2	1.13 (0.82 – 1.06)	1.02 (0.89 – 1.17)	1.35 (0.97 – 1.89)
Rural*Q3	1.26 (0.92 – 1.04)	1.28 (1.07 – 1.51)	1.57 (1.07 – 2.31)
Rural*Q4	1.03 (0.77 – 0.94)	1.06 (0.84 – 1.32)	1.92 (1.22 – 3.02)
Rural*Q5	1.34 (0.98 – 1.03)	1.12 (0.94 – 1.34)	1.52 (0.91 – 2.56)
SESi*$PM_{2.5}$ quintile			
SESi*Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)
SESi*Q2	0.92 (0.80 – 1.06)	0.98 (0.91 – 1.05)	0.92 (0.77 – 1.10)
SESi*Q3	0.91 (0.80 – 1.04)	0.90 (0.84 – 0.97)	0.81 (0.69 – 0.96)
SESi*Q4	0.82 (0.72 – 0.94)	0.89 (0.83 – 0.96)	0.73 (0.62 – 0.86)
SESi*Q5	0.91 (0.80 – 1.03)	0.93 (0.87 – 1.00)	0.88 (0.76 – 1.03)
Rural*SESi	1.21 (1.04 – 1.41)	1.05 (0.96 – 1.14)	1.33 (1.08 – 1.63)

Model adjusted for: maternal age, nulliparous, drug or alcohol flag, maternal smoking, season of birth, DA-level education, DA-level Asian immigrant density, First Nation on-

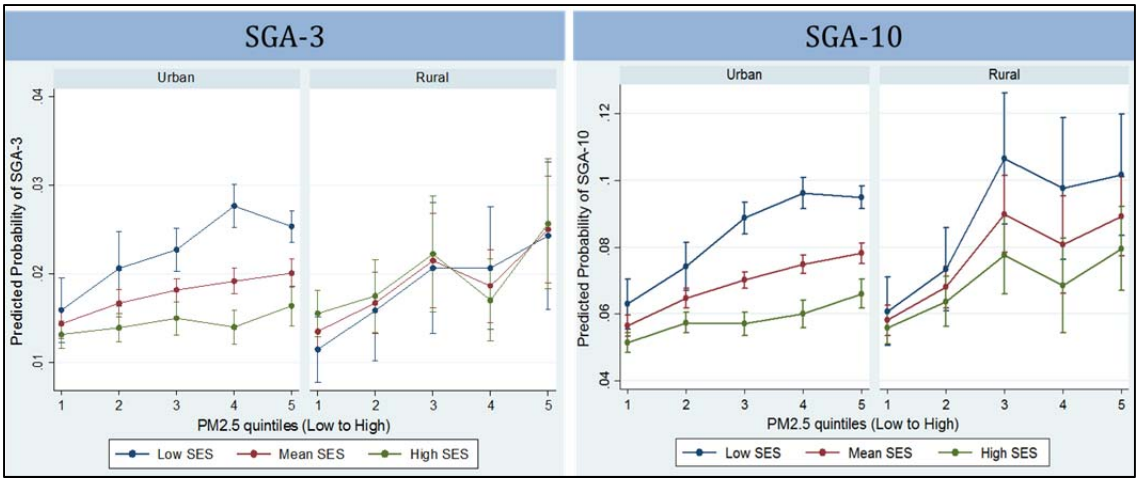


Figure 3: Predicted probabilities with 95% CIs from SGA-3 model-2 (SGA-3-m2) and SGA-10 model-2 (SGA-10-m2)

Term Low Birth Weight (tLBW)

Table 1 shows the results for tLBW from an interaction model between $PM_{2.5}$, SES and urban-rural residence. The predicted probabilities derived from these models are presented in Figure 4 using two different variable perspectives. Similar to SGA, these models show is that rising $PM_{2.5}$ always increases the risk of tLBW, and that this risk is modestly tempered by rising SES, but only in urban areas (Figure 4A). Interesting, rural areas show a reversal of the SES association such that higher SES neighbourhoods demonstrate a larger risk of tLBW compared to low SES neighbourhoods. This trend was partially evident for SGA-3, but the wide confidence intervals obscured the relationship. The explanation for this observation is unclear; however, it could be related to the size of the DAs in rural areas which encompass a geographic area much larger than a typical neighbourhood. A similar finding was observed by Auger et al (2009) which showed that remote rural areas were associated with adverse birth outcomes among university educated mothers only [8].

The MOR for tLBW (Table 1) signify that, in the median case, a randomly selected individual moving from a low risk DA to a higher risk DA will realize a 15% increased risk of tLBW, MOR 95% CI: 1.15 (1.04 – 1.76). Thus, after adjusting for individual and neighbourhood-level known risk factors, a person's residential neighbourhood still carries a good degree of relevance to their risk of tLBW.

Non-linear specifications of $PM_{2.5}$ were also tested conditional on SES and urban-rural residence. The quatradic expression of the continuous $PM_{2.5}$ was not significant, but the quinile transformation did show indication of non-linearity (Table 2 and Figure 4B). For

urban areas, there was clear modification of the $PM_{2.5}$ association by SES on the risk of tLBW. For rural areas, there was a consistent increase in risk of tLBW with rising $PM_{2.5}$ levels, but showed no statistically significant distinction across the levels of SES. The 4th quintile for PM2.5 displays an anomaly in its effect estimation, likely due to small numbers within the strtifications. These results are consisent with the findings presented in the endnote for Chapter 4, demonstrating that the mechanisms that operate through neighbourhood low SES to affect fetal growth are more strongly experienced within urban areas where the relative disparities are more pronounced [7].

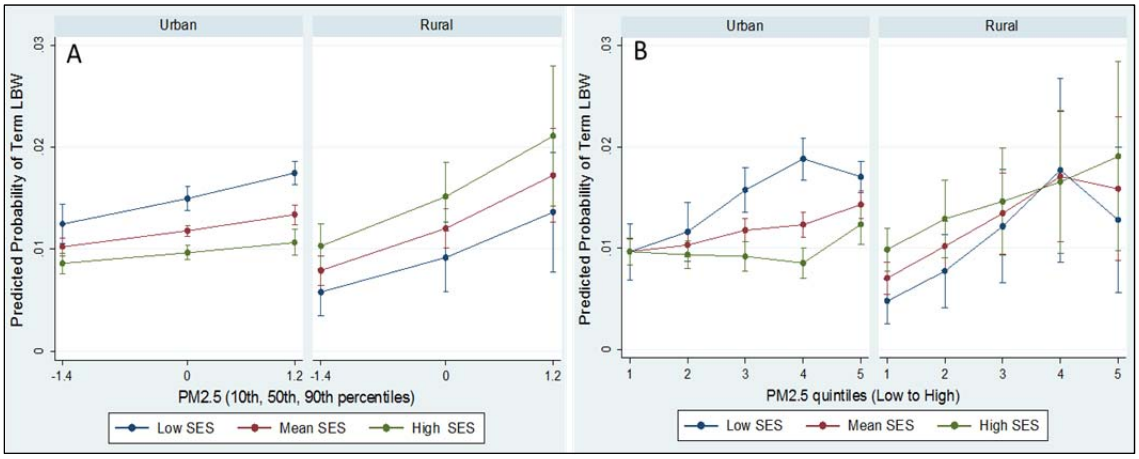


Figure 4: Two different perspectives of the same model
Plot A and B show the predicted probabilities with 95% CIs from tLBW model-1 in Table 1 (tLBW-m1).

Intra-uterine Growth Restriction (IUGR)

Unlike the other measures of adverse fetal growth (tLBW SGA-3, SGA-10), IUGR shows a protective association with rural residence in Figure 1. This could be why IUGR did not demonstrate any trend (statistically significant or otherwise) of effect heterogeneity between urban and rural births with respect to SES and $PM_{2.5}$. The explanation of this finding is unclear; however, it could be due to regional differences in the completion of BC perinatal forms and maternal charts. IUGR did demonstrate to have a non-linear association with $PM_{2.5}$, and a significant interaction between SES and $PM_{2.5}$. This interaction was not present when $PM_{2.5}$ was modeled as a linear effect (Table 4 and Figure 5).

The MOR for IUGR (Table 4) signifies that, in the median case, a randomly selected individual moving from a low risk DA to a higher risk DA will realize a 34% increased risk of IUGR, MOR 95% CI: 1.34 (1.26 – 1.46). This is a fairly large MOR, even after adjusting for the individual and neighbourhood-level risk factors, and suggests that a substantial portion of the between-DA variance is left unexplained.

Table 4: ORs for gestational diabetes in relation to $PM_{2.5}$, SES, and Rural Residence

	IUGR SES*$PM_{2.5}$ OR (95%CI)
$PM_{2.5}$	1.17 (1.12 – 1.22)
$PM_{2.5}$* $PM_{2.5}$	0.93 (0.91 – 0.96)
SESi	0.90 (0.86 – 0.93)
Rural Residence	0.75 (0.66 – 0.86)
Immigrant Density	1.07 (1.04 – 1.10)
Higher Education	0.96 (0.93 – 1.00)
SESi*$PM_{2.5}$	0.95 (0.91 – 0.99)
Rural*SESi	--
Rural* $PM_{2.5}$	--
Multilevel Model Outputs	
Intercept	0.013
Random intercept Variance	0.096
Median OR (95% CI)	1.34 (1.26 – 1.46)

Logistic random intercept models adjusted for: maternal age, nulliparous, drug or alcohol flag, maternal smoking; season of birth, First Nation on-reserve birth.

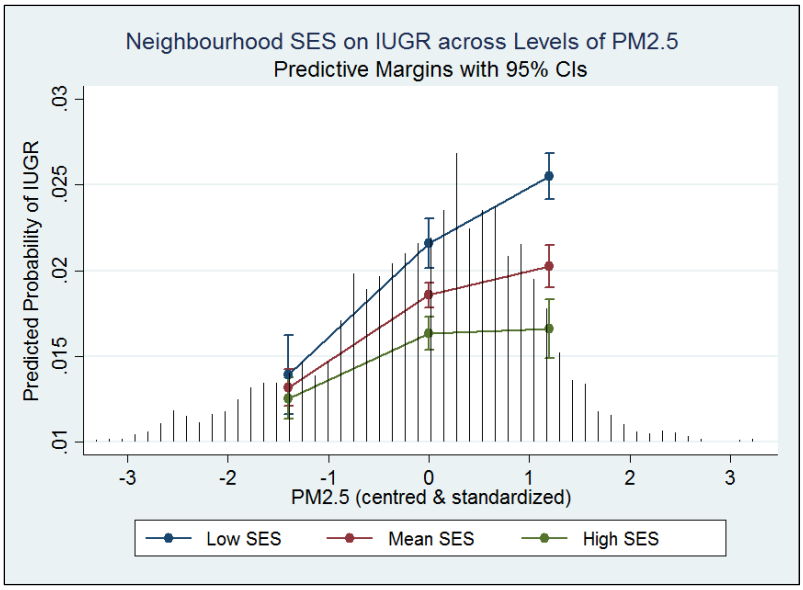


Figure 5: Predicted probabilities with 95% CIs from SGA-3 model-2 (SGA-3-m2) and SGA-10 model-2 (SGA-10-m2)

Preterm Birth (PTB)

Preterm birth is defined as a birth which reached a minimum gestational age of 37 completed weeks. After exclusions, there were 231,970 singleton (live and stillborn) births located in located in 6,338 neighbourhood DAs (min. = 1, max. = 781, avg. = 36). Excluded observations included: births with missing gestational age <37 weeks (378), missing cigarettes/day (n = 2,501), and missing $PM_{2.5}$ (n = 1,511). PTB was categorized by its severity based on gestational age (mild: 34 to 36 weeks, moderate: 32 to 33 weeks, early: 28 to 31 weeks, and very early: < 28 weeks).

Figure 6 shows the results from a partial proportional odds (pp-odds) regression model (similar to an ologit regression but allows the coefficients for the parameters to vary between the levels of the categorical dependent variable) [9]. The pp-odds model allows the researcher to see which variables have a constant risk across all levels of PTB severity and which ones have varying importance. The bottom three sets of variables listed under the different PTB severities have varying risks. While some variables change very little (e.g. nulliparous), others have greater variation (e.g. gestational hypertension).

The risk of $PM_{2.5}$ was shown to have a small but significant protective association for PTB risk. This association is constant for all PTB severity sub-types. The association for SES on the otherhand shows a clear trend of increasing protective associtions with the more severe PTB sub-types. PTB is a complex birth outcome with many underlying risk factors. Further research into the observed relationship between PTB and $PM_{2.5}$ needs to be explored for potential bias [10, 11].

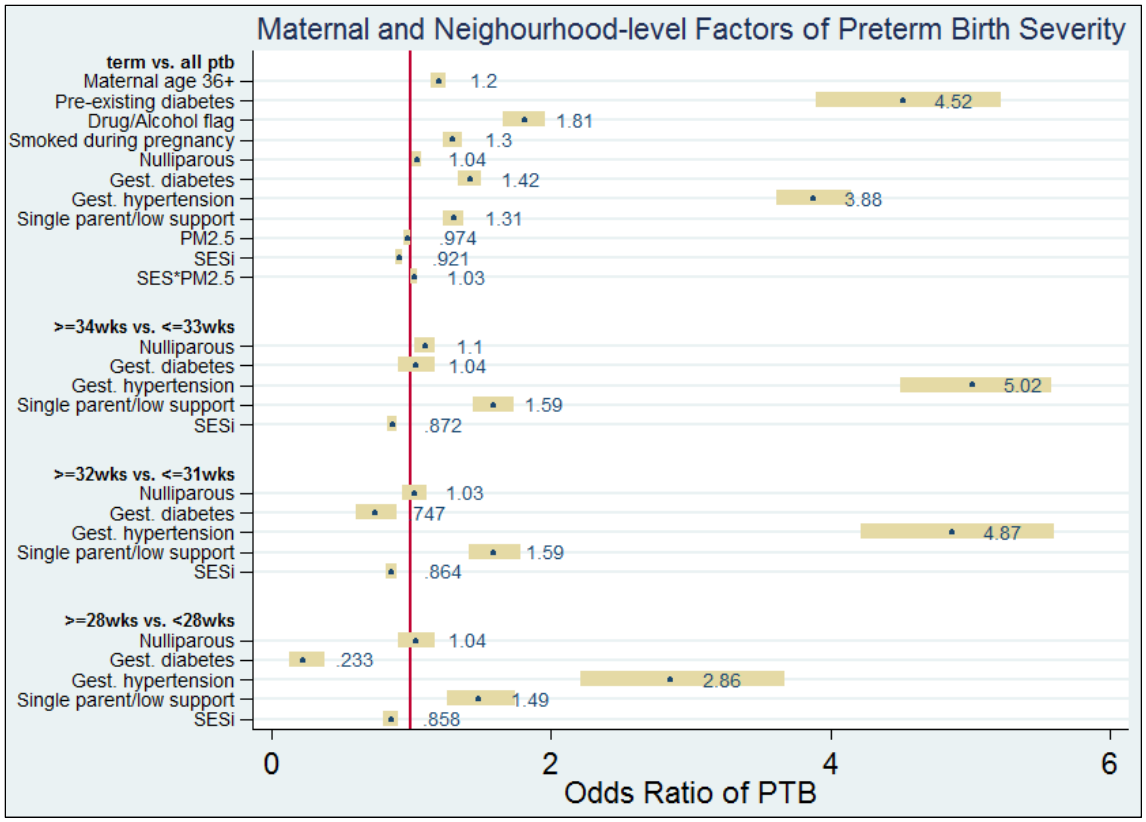


Figure 6: Adjusted ORs and 95% CI range (shaded regions) for maternal and neighbourhood-level factors associted with the severity of PTB risk.

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