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Examining Neighbourhood Socioeconomic Status, Anxiety and Depression during Pregnancy, and Preterm Birth

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Examining Neighbourhood Socioeconomic Status, Anxiety and Depression during Pregnancy, and Preterm Birth

by

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Abstract

Background

Understanding of influence of anxiety, depression, and neighbourhood socioeconomic status (SES) on the risk of preterm birth (PTB) is unclear. This doctoral research examined the ability of neighbourhood SES to predict the risk of PTB, the utility of existing anxiety scales in measuring anxiety in pregnancy, and whether neighbourhood SES modified the association between anxiety and depression during pregnancy and PTB.

Methods

This study used data from two pregnancy cohort studies in Alberta, Canada (n=5,528). The data were linked to neighbourhood SES data, derived from the Canadian census. A multilevel logistic regression prediction model was developed to examine whether neighbourhood SES improves the prediction of PTB. Confirmatory factor analysis and Spearman correlation were used to examine the utility of anxiety scales in pregnancy. A multivariable logistic regression model was used to assess whether neighbourhood SES modifies the association between anxiety and/or depression and PTB.

Results

Neighbourhood level variance explained PTB by 6%. Neighbourhood SES combined with maternal characteristics predicted PTB with an area under the receiver operating characteristic curve (AUC) of 0.75. Maternal characteristics alone had AUC of 0.60. The model fit of anxiety scales ranged from inadequate to adequate. The correlation between the scales was low to

moderate. The presence of both anxiety and depression, but neither anxiety nor depression alone, was significantly associated with PTB (OR=1.57, 95% CI=1.07, 2.29) and had significant interaction with neighbourhood deprivation (p-value=0.014).

Conclusions

This research may suggest that women's neighbourhood SES improves overall prediction of PTB and that it modifies the effects of anxiety and depression on risk of PTB. It may also indicate that existing anxiety scales do not measure anxiety as a single dimension and they are incomparable. These findings may guide the identification of women at increased risk for PTB and future research in the field.

Preface

This doctoral dissertation comprises three manuscripts, the first one of which has been published, and the other two are currently under revision. Each of the co-authors has provided permission for the manuscripts to be included in this dissertation. Please see the details as to the contribution of each of the authors for the three manuscripts.

Chapter 3: Adhikari K, Patten SB, Williamson T, Patel AB, Premji S, Tough S, Letourneau N, Giesbrecht G, Metcalfe A. Does Neighbourhood Socioeconomic Status Predict the Risk of Preterm Birth? A Community-based Canadian Cohort Study. BMJ Open 2019;9:e025341. doi:10.1136/bmjopen-2018-025341.

Chapter 4: Adhikari K, Patten SB, Williamson T, Patel AB, Premji S, Tough S, Letourneau N, Giesbrecht G, Metcalfe A. Assessment of Anxiety during Pregnancy Using Multiple Anxiety Scales: Do Anxiety Scales Differ in Their Ability to Assess Anxiety During Pregnancy? Submitted to Journal of Psychosomatic Obstetrics & Gynecology (submitted: March 2019).

Chapter 5: Adhikari K, Patten SB, Williamson T, Patel AB, Premji S, Tough S, Letourneau N, Giesbrecht G, Metcalfe A. Neighbourhood Socioeconomic Status Modifies the Association between Anxiety and Depression during Pregnancy and Preterm Birth: A Community-based Canadian Cohort Study. Submitted to Journal of Community Health and Epidemiology (submitted: April 2019).

Kamala Adhikari was involved in the conception and design of the study. Kamala was also responsible for conducting the analysis, interpreting the data, and drafting these three manuscripts. Amy Metcalfe provided overall supervision to Kamala in conducting this study and contributed to conception and study design, interpretation of data, provided intellectual content and revisions to the manuscripts. Scott B Patten co-supervised Kamala and contributed to each stage of the study and provided critical input to the manuscripts. Tyler Williamson and Alka B Patel were involved in the conception and design of the study and provided interpretation and intellectual content to the manuscripts. Shahirose Premji, Suzanne Tough, Nicole Letourneau, and Gerald Giesbrecht provided interpretation and intellectual content to the subsequent draft of the manuscripts. All authors read and approved the final manuscripts.

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“It is time to refocus, reinforce, and repeat the message that health disparities exist and that the health equity benefits everyone”

Kathleen G. Sebelius

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List of Abbreviations

AOF: All Our Families

APrON: Alberta Pregnancy Outcomes and Nutrition

AUC: Area Under the Receiver Operating Characteristic Curve

CFI: Comparative Fit Index

CI: Confidence Interval

DA: Dissemination Area

DSM: Diagnostic and Statistical Manual of Mental Disorders

EPDS: Edinburgh Postnatal Depression Scale

EPDS-3A: Edinburgh Postnatal Depression Scale Anxiety Subscale

ICC: Intra-Cluster Correlation

IQR: Interquartile Range

LR+: Positive Likelihood Ratio

LR-: Negative Likelihood Ratio

MOR: Median Odds Ratio

NPV: Negative Predictive Value

OR: Odds ratio

PPV: Positive Predictive Value

PTB: Preterm Birth

r: Correlation

RMSEA: Root Mean Squared Error of Approximation

SAGE: Secondary Analysis to Generate Evidence

SCL-90: Symptoms Checklist-90

SES: Socioeconomic Status

SEM: Structural Equation Modeling

SRMR: Standardized Root Mean Squared Residual

STAI: State Trait Anxiety Inventory

STAI-S: State Trait Anxiety Inventory-State

TLI: Tucker Lewis Fit Index

Chapter 1: Introduction

Preterm birth (PTB) is responsible for 35% of neonatal deaths globally (1). Among survivors, PTB is also a significant risk factor for short- and long-term morbidities, such as respiratory distress syndrome, cerebral palsy, developmental delay, and learning difficulties (2-4). In Canada, the current PTB rate is 7.8% (5), resulting in an annual economic burden of $587 million (2), with Alberta having the second highest provincial PTB rate (8.7%) (5). Despite substantial clinical research and interventions to prevent PTB, the incidence of PTB has not been reduced in Canada or globally (5, 6). Thus, this doctoral research examined selected modifiable risk factors for PTB, particularly neighbourhood level socioeconomic status, and anxiety/depression during pregnancy. The goal of this research was to identify women at increased risk for PTB, which ultimately may assist in the allocation of resources and reduce the incidence of PTB.

Literature was reviewed using a general approach. Published papers related to this doctoral thesis were searched in PubMed and Google Scholar electronic databases using keywords, with no limitation to the year of publication. The included keywords were related to “preterm birth”, “risk factors of preterm” “socioeconomic status (individual level or neighborhood level or area level)”, “anxiety during pregnancy” “depression during pregnancy”, anxiety and depression during pregnancy, and “measurement of anxiety and depression”. The keywords were used separately or were combined, as needed, using OR and AND to identify relevant papers. The papers were read thoroughly, critiqued, and synthesized/summarized to identify the research gaps as follows.

Preterm Birth

The World Health Organization defines PTB as any birth before 37 completed weeks of gestation, or fewer than 259 days since the first day of the women's last menstrual period (7). PTB is classified as extremely preterm (<28 weeks' gestation), very preterm (28 to <32 weeks' gestation), moderate preterm (32 to <34 weeks' gestation), and late preterm (34 to <37 weeks' gestation) (8). Among them, late PTB is the most common subgroup of PTB, comprising approximately 80% of all PTBs (9, 10). Generally, 30-35% of PTBs are medically indicated and 65-70% are spontaneous (11).

PTB is an important public health concern. Worldwide, a total of 15 million births are preterm with a global average rate of 11.1% (95% CI=9.1%, 13.4%) (6). The rate of PTB continues to rise in many high-income countries including Canada, the United States, and European nations where current rates range from 5 to 12% (6). Infants who are born preterm are at a greater risk than infants who are born at term for mortality and a variety of morbidities and developmental problems (3). PTB is the leading cause of newborn deaths, and the second leading cause of death, after pneumonia, in children under the age of 5 (1, 3, 12). It is a significant risk factor for lifelong morbidity, such as developmental delay, learning difficulties, cerebral palsy, blindness, and deafness (4, 13-18). These problems contribute to the medical, economic, and social costs of PTB (2, 3). Premature infants tend to remain longer in hospital, which affects the cost to the health care system. In the United States, the average medical cost including both inpatient and outpatient care was 10 times greater for preterm than for term births (12). In Canada, the Canadian Institute for Health Information estimates that in-hospital cost for preterm infants is

nine times higher than for full-term infants. Moreover, the total long-term health care costs of PTB are estimated to be $13.3 billion per year in Canada (19). In addition to the medical costs, preterm infants require significant attention, time and care from their family, schools, and public services as they may require special monitoring and care throughout their growth, development, and education (3, 19). Thus, PTB influences not only a child's health, but also the wellbeing and quality of life of the entire family.

Despite the personal and societal burden of PTB, its cause is poorly understood. PTB may be initiated by multiple mechanisms such as infection, stress, uterine over-distension, utero-placental ischemia, and hormonal and immunological mediating processes (11, 20). As the mechanisms or causes of PTB are complex and may not be possible to establish in most cases, much research attention has focused on risk factors associated with PTB, with the aim of identifying pregnant women at increased risk of PTB, and relevant early interventions to prevent PTB.

PTB has multiple risk factors, which are interconnected to each other and are heterogeneous depending on whether the PTB is spontaneous or medically indicated (3, 20, 21). Potential risk factors for spontaneous PTB include: increased maternal age, multiple gestation, infection (e.g., urinary tract infections, malaria, bacterial vaginitis, Human Immunodeficiency Virus infection), lifestyle factors (smoking, excessive alcohol consumption), nutritional status, underlying maternal chronic medical conditions (e.g., diabetes, hypertension, anemia, asthma, thyroid disease), less access to health services, intimate partner violence, short inter-pregnancy

interval, maternal psychological health, and biological and genetic factors (3, 20, 21). Medically indicated PTBs are associated with maternal and fetal characteristics, such as hypertension, preeclampsia, diabetes mellitus, placental abruption, obesity, fetal distress, fetal growth restriction, fetal congenital abnormalities (e.g., anencephaly) (3, 20, 21). Additionally, the increasing trend of PTB in recent years, mostly in high income countries, is related to the increasing rate of maternal obesity, advanced maternal age, and multiple pregnancy due in part to increased use of assisted conception (3). Importantly, the most of these risk factors are more prevalent among pregnant women with low socioeconomic status (SES) (20). Thus, prevention of PTB may not be possible without directing efforts to address the effect of low socioeconomic status.

Socioeconomic Status

Individual Level Socioeconomic Status

Individual level SES refers to an individual's economic and social position, usually measured by income, education, and employment (22). Individual level SES increases the risk of poor health outcomes, such as PTB, through material deprivation or psychosocial distress (22, 23). An individual's SES relates directly to material conditions, which has significant implications on access to social and economic resources. For example, fulfilling one's daily needs (e.g., location and condition of housing, food intake or avoidance of hunger, clothing, and transportation) and access to resources (e.g., use of health services and opportunities to access cultural, recreational, and physical activities) (22). Facing challenges in daily life that are linked to material deprivation may also create chronic stress (23). Similarly, an individual's SES relates to

psychosocial distress, as people from low socioeconomic groups tend to compare themselves with other people (i.e., who have relatively higher socioeconomic status) in society, which leads to high levels of psychosocial stress, decreased social integration and networking, and increased feelings of shame and worthless (23). Additionally, SES has an intergenerational transmission that affects health in a life course perspective, such as SES of parent influencing the development of the fetus in utero, birth outcomes, and the child's growth, learning and behaviors, and subsequent SES (22).

Neighbourhood Socioeconomic Status and Preterm Birth

Neighbourhood SES is an area level measure of socioeconomic status, which aggregates individual-level SES (such as income, education, and employment status) at a certain geographical level (24). It reflects the social and economic development of the residential area and identifies groups who experience disadvantage compared with others in nearby communities (25, 26). Neighbourhood SES may influence an individuals' health by determining their exposure to health benefitting or risk elevating factors. For example, low neighbourhood SES may negatively affect an individual's ability to fulfill daily needs, access resources, make lifestyle choices, and cope with different situations, which may happen due to unequitable distribution of resources across neighbourhoods (22, 24, 27, 28). Neighbourhood SES is often measured by three individual measures of income, education, and employment status or a composite of these measures aggregated up to the neighbourhood level (22, 29). The Pamaplon deprivation index, an area level socioeconomic measure, is a composite score that comprises the proportion of persons without high school diplomas (education), the average personal

income (income), and the rate of unemployment (employment) within the dissemination area (DA) level (25). The index has been recognized as a valid measure of area level SES in Canada (25, 30, 31), and has been widely used to determine health resource allocation policies in Canada (26). However, area level socioeconomic measures can serve as both a proxy measure of individual's SES in that particular geographical area, as well as characterizing the SES of that area itself (22).

Several studies, including systematic reviews, have found that globally the incidence of PTB is inversely associated with neighbourhood SES (32-35): pregnant women living in neighbourhoods with low SES tend to have higher rates of PTB (8-13). The high rate of PTB in neighbourhoods with low SES may not only relate to the fact that women living in these neighbourhoods have higher individual level risk factors (such as smoking, unhealthy eating habits, obesity) for PTB. It may also relate to the neighbourhoods themselves, or the unfavorable influence of living in lower socioeconomic neighbourhoods (22, 24, 27). Furthermore, it has been also reported in the literature that individual level risk factors are also determined by residential context (24, 27). For example, women living in low socioeconomic neighbourhoods may be less likely to adopt healthy lifestyles due to poor access to leisure centres and healthy foods. This makes them adopt unhealthy lifestyles such as unhealthy eating habits and being physically inactive, which leads to obesity. In addition, growing research in the general population also supports the findings that poor health outcomes occur more frequently in individuals who live in poor or disadvantaged neighbourhoods compared to those who live in more advantaged neighbourhoods (22, 24, 36, 37). Nonetheless, the existing finding on the

relationship between neighbourhood SES and PTB is inconclusive due to some methodological limitations.

The first methodological issue in the examination of the association between neighbourhood SES and PTB is related to the measurement of neighbourhood socioeconomic status. The majority of existing studies examining the association between neighbourhood SES and PTB have used income (usually median household income), while a few others have used either education status (usually highest education level completed) or employment status (usually employed/unemployed) or material deprivation index (a composite score) as a measure of neighbourhood SES (32, 35). Median household income, however, may not fully explain the relationship between area level SES and PTB; instead, the material deprivation index which captures income, education, and employment status may be a better predictor (25, 30, 31). While both median household income and deprivation index are aggregated at a certain geographical level, the material deprivation index is a validated broader measure of area level SES compared to income alone. Furthermore, most previous studies have identified a small effect or no effect of area level SES on PTB. For example, the odds ratios for PTB in 3 Canadian studies, conducted in British Columbia, Quebec, and Nova Scotia, ranged from 1.11 (95% CI= 1.04, 1.19) to 1.26 (95% CI= 1.17 and 1.35) for women residing in the lowest income area relative to the highest income area (34, 38, 39). A Canadian study conducted at national level showed no effects of area level SES on PTB (33). This weak association may be related to how area level SES was measured (i.e., by income alone) in these studies. There remains a gap in understanding on whether neighbourhood SES measured by area level deprivation index is a

better predictor of PTB than the neighbourhood SES measured by area level median household income.

The second methodological issue in previous studies relates to their inability to distinguish whether the association between area level SES and PTB resulted from the influence of SES at the "individual level" or "area level" or "mix of both levels". This problem is generally related to data insufficiency. The majority of previous studies relied on administrative databases, which often lack important data on potential modifiers/confounders, such as maternal SES (maternal income, education, and employment), lifestyle or risk behaviors, obstetric history, and social support. Accordingly, earlier studies were unable to control for those important individual level factors, including maternal socioeconomic status. Therefore, the study findings might be confounded by the effect of those factors. Furthermore, area level SES and individual level SES may not agree with each other (particularly in urban neighbourhoods that are undergoing gentrification), and using area level SES as a proxy of individual SES may bias the association (40). Also, the effect of an individual's SES on health may be altered by the SES of area where that individual lives (40). As a result, it is important to include variables related to both area level and individual-level SES in the analysis.

Another methodological problem is the use of inappropriate analytical methods. Multilevel analysis is an appropriate analytical approach for the hierarchical nature of data to control for data at multiple levels. It does not assume independence of the observations, and accounts for the variation between and within groups or areas (41, 42). However, most of the previous

studies used inappropriate analysis methods for addressing clustered data (i.e., classical logistic regression which assumes independence of observations). This critical issue is more common in Canadian studies. A systematic review on association between area level SES and PTB did not include a single Canadian study; one reason for this was inappropriate analytical methods used (i.e., not using multilevel analysis) in previous studies (32).

While many studies have examined the association between neighbourhood SES and PTB (32, 33, 35), our understanding about the ability of neighbourhood SES to predict the risk of PTB is limited. Examining the association between neighbourhood SES and PTB informs the independent contribution of individual risk factors on the risk of PTB, whereas prediction of PTB based on neighbourhood SES informs the future probability of giving PTB based on the patterns of combined set of risk factors (43-45). Furthermore, even strongly associated risk factors can have a low capacity to discriminate PTB in the population (45-47). To illustrate, well-recognized individual level risk factors (such as previous PTB and body mass index) for PTB have shown a low discriminatory accuracy in predicting PTB (46, 47). Discriminatory accuracy refers to the ability of a predictive model to discriminate between those who experience, and those who do not experience PTB (44, 48). Additionally, a statistically significant association between neighbourhood SES and PTB may exist, with small or no variation of PTB at neighbourhood level (49-51). Thus, the association may provide unreliable information about the likelihood of delivering preterm infants among women living in certain neighbourhoods (49, 50). The use of valid prediction models may help to effectively identify women at high risk of delivering

preterm infants, and in planning suitable public health interventions targeting women at increased risk.

Keeping this in mind, this research aimed to develop and internally validate a prediction model to examine the ability of neighbourhood level SES to predict PTB. The research compared the predictive ability of the model that includes both neighbourhood level SES along with maternal individual characteristics and the model that includes maternal characteristics alone. In addition, the research elucidated the utility of neighbourhood median income and material deprivation index as measures of neighbourhood socioeconomic status.

Anxiety during Pregnancy

The American Psychological Association defines anxiety as an emotion characterized by feelings of tension, recurring (worried, intrusive) thoughts, and physical changes, such as sweating, trembling, dizziness, and a rapid heartbeat (52). Pregnant women may experience anxiety symptoms more often than non-pregnant women due to pregnancy being a time of intense physical, physiological, and psychological changes (53). Anxiety symptoms experienced by pregnant women can be related to general anxiety or pregnancy-specific anxiety. Anxiety during pregnancy (which refers to general anxiety throughout this research, unless pregnancy-specific anxiety is explicitly mentioned) is one of the most common forms of psychosocial distress during pregnancy (54, 55). In the United States, a prospective study reported the prevalence of anxiety to range from 12% to 18% (56), and a longitudinal study reported that 54% of women have anxiety symptoms at some point during pregnancy (54). In Canada, the

prevalence of anxiety also varies from study to study, affecting from 15.5% to 27% of pregnant women (55, 57, 58).

Measurement of Anxiety during Pregnancy

Semi-structured diagnostic clinical interviews are considered the reference standard for the diagnosis of anxiety disorders. However, they require well-trained mental health professionals and a long time (typically 30 minutes to 3 hours) to conduct (59). Therefore, interviews are impractical to use for screening purpose in busy clinical settings (59). In contrast, self-reported anxiety scales, such as the State Trait Anxiety Inventory (STAI), the General Health Questionnaire, the Hospital Anxiety and Depression Scales, the Beck Anxiety Inventory, the Perinatal Anxiety Screening Scale, the Edinburgh Postnatal Depression Scale Anxiety Subscale (EPDS-3A), and the Symptoms Checklist (SCL)-90, are simple, short, and less expensive to implement in clinical and research settings (60, 61). As such, they are more commonly used to screen women for anxiety symptoms during the perinatal period (60, 62). While these instruments are not diagnostic interviews, their use is expected to be consistent with the goals of screening, as they are designed to facilitate the earlier detection, assessment, and treatment of anxiety disorders. However, most anxiety scales that are used in pregnancy were developed for general populations, and very few anxiety scales have been validated in pregnant populations (60, 61, 63). Studies, including systematic reviews, assessing the validity of self-reported anxiety scales in perinatal populations (60, 61, 63-65) are inconclusive on whether these scales are valid for anxiety screening in perinatal populations and do not clearly recommend one scale as being superior to the others, whereas the EPDS addresses this gap for

the measurement of depression. The validity of these scales in pregnant populations is important as the scale may be contaminated by the aspects of pregnancy itself. For example, many common signs and symptoms of pregnancy are similar to common signs and symptoms of anxiety (e.g., difficulty sleeping and feeling uncomfortable), potentially affecting the utility of anxiety screening tools in pregnant women.

Some of the commonly used anxiety scales to assess anxiety in pregnant women include the State Trait Anxiety Inventory-State (STAI-S), SCL-90, and EPDS-3A. The STAI-S is a 20-item self-reported anxiety scale, with each item ranging from 1 “not at all” to 4 “very much” (66). It evaluates current feeling of tension, anxiety, nervousness, and difficulties. It is the most commonly used measure of general anxiety in perinatal populations (60, 61) with a sensitivity of 80.95% and a specificity of 75.75% (60, 67). The standard cut-off of ≥40 out of a maximum of 80 SAI score is used to define the presence of clinically significant anxiety during pregnancy (60, 67). The STAI-6 scale is a short form of STAI-S containing six items (items 1, 3, 6, 15, 16, and 17 on the STAI full scale) has been reported by Marteau et al as a valid measure of anxiety in pregnant populations (68). The cut-off for the STAI-6 to classify an individual at increased risk of clinically significant levels of anxiety has not been identified. The SCL-90 anxiety subscale is a 10 item self-reported scale, with each item ranging from 0 “not at all” to 4 “extremely” with a total possible score of 40 (69, 70). Using the Derogatis criteria, the SCL-90 scale uses a mean score for each participant that is converted into normative T scores (71-73). The SCL-90 scale is a valid measure of general anxiety and a T score of ≥63 is considered as clinically significant levels of anxiety (72, 73). While the EPDS was specifically designed to assess depression, three items

(items 3, 4, and 5), comprising the anxiety subscale (EPDS-3A), have been suggested as a measure of anxiety during pregnancy (74, 75) with a sensitivity of 66.70% and a specificity of 88.2% in the obstetric population (75). The standard cut-off of ≥6 out of a maximum of 9 EPDS-3A scores is used to define the presence of clinically significant anxiety during pregnancy (75). However, the priori specified factor structure for these anxiety scales (except the SAI-6) has not been confirmed in pregnant women.

Pregnancy-specific anxiety is being acknowledged as a distinct syndrome, which consists of concerns related to giving birth, the health of the fetus, physical appearance, and hospitalization during and after childbirth (64, 76). Accordingly, several pregnancy-specific anxiety scales have been newly constructed (64). However, the performance of the pregnancy-specific anxiety scales to detect anxiety during pregnancy remains unclear, and their use is often limited in research and in clinical settings (64). Furthermore, as these scales are specifically relevant to pregnancy-specific anxiety, they may not capture the broad range of clinically significant anxiety symptoms (77).

Overall, the assessment of anxiety during pregnancy may enhance recognition of anxiety, and thereby connect women with anxiety symptoms to appropriate health interventions or referral services. As no consensus exists regarding the most suitable anxiety screening scale for use during pregnancy, different anxiety scales (specifically, self-reported general anxiety scales) have been used to measure anxiety during pregnancy (60, 61, 63-65). The use of a variety of anxiety scales can hamper the comparability of results (62). As such, there is a wide variation in

the prevalence estimates of anxiety during pregnancy and inconsistencies in its association with adverse pregnancy outcomes and child development in the literature (54, 57, 78-82). Additionally, information about the performance of these scales in measuring anxiety during pregnancy is limited. Thus, this doctoral research aimed to evaluate multiple anxiety scales in the same sample of pregnant women to elucidate the suitability and comparability of self-reported anxiety scales in measuring anxiety during pregnancy.

Depression during pregnancy

Depression is a mood disorder, characterized by feeling of sadness and/or a loss of interest in activities once enjoyed (83). Depression can lead to distress, dysfunction, and danger in human body and mind, and results in clinically recognizable physical and psychological symptoms (83). It can severely reduce an individual's ability to perform daily life- and job-related activities (83). Depression is one of the most common psychiatric disorders in women of childbearing age (84-86). Approximately, one in five women experience a depressive disorder during their lifetime (85, 87), with 10% meeting diagnostic criteria for a depressive disorder at some point during pregnancy (88). Similarly, 37% of women experience depression symptoms at some point during pregnancy (54).

Measurement of Depression during Pregnancy

There are several self-reported screening scales to measure depression during pregnancy, such as the Hospital Anxiety and Depression Scale, the Beck Depression Inventory, and the EPDS (89). The EPDS is a widely accepted and the most common screening tool used to measure

antenatal and postnatal depression (89). The EPDS is a 10-item self-rating scale with each item ranging from 0 to 3 to assess the symptoms of current depression – how women have felt in the past 7 days (90). The EPDS has high internal consistency of 0.87 (90), a sensitivity of 78%, and specificity of 99% in the perinatal population (91, 92). The standard cut-off score of ≥13 out of 30 points on the EPDS is used to define the presence of clinically significant depression during pregnancy and the postpartum period (93).

Anxiety and Depression during Pregnancy and Preterm Birth

Evidence supports that anxiety and depression during pregnancy lead to poor birth outcomes, such as PTB, low birth weight, and postnatal depression (80, 94-96). Mothers suffering from anxiety and depression are less responsive, interactive, and attached to their infants (97), which can influence their children's behavioral and cognitive development (98).

It is plausible that anxiety and depression during pregnancy increase the risk of PTB through biological mechanisms and/or maternal behavioral process (11, 20, 99-101). Anxiety and depression, characterized by psychosocial distress, is linked to the alternation of hypothalamic-pituitary-axis (leading to hormonal changes, e.g., cortisol and corticotrophin-releasing hormone), the dysregulation of inflammatory biomarkers (e.g., cytokinese), and immunological impairment (99-101). Likewise, women with psychosocial distress are more likely to engage in adverse behaviors such as smoking, alcohol abuse, eating unhealthy foods, not receiving adequate prenatal care or low self-care (20). These factors may link anxiety and depression to PTB (11, 20, 99-101). However, the association between anxiety and depression during

pregnancy and PTB is incompletely understood due to gaps in three aspects.

Firstly, the association, specifically, between anxiety during pregnancy and PTB is inconsistently reported in the literature (79-82). For example, two recent systematic reviews and meta-analyses concluded that there is a significant association between anxiety and PTB, although half of the individual studies included in these reviews have reported a nonsignificant or imprecise association (80, 82). Another two previous systematic reviews and meta-analyses reported no association between the levels of anxiety and PTB (79, 81). These contradictory findings make it difficult to derive a definitive conclusion about the effect of anxiety during pregnancy on PTB.

Secondly, most of the previous studies examining the association between anxiety and depression during pregnancy and PTB were conducted in a medical setting (i.e. hospital or clinic) with a small sample, and high rates of attrition (80, 82, 102). This may lead to selection bias, limited generalizability, and imprecise results. Some of these studies did not adjust for important confounding variables such as body mass index and smoking (101, 103, 104); hence, the relationship between anxiety and depression during pregnancy and birth outcomes might have been confounded by those variables. And, some studies were unable to distinguish depression or anxiety given the measurement tool used (105, 106) or some have measured anxiety status of pregnant women through maternal recall during the postpartum period, and thus may have suffered from misclassification bias.

Third, anxiety and depression often co-occur. Presence of both anxiety and depression is the most common psychological condition, which impacts up to 50% of women with anxiety or depression (107). Women who have both anxiety and depression are more likely to have severe anxiety and depression symptoms than those with isolated anxiety or depression (108); thus, substantially increasing the risk of poor birth outcomes, including PTB, in this group of women (103, 108). However, most of the previous studies analyzed the association between anxiety or depression and PTB without considering that both anxiety and depression may be present or analyzed isolated anxiety or depression intermixing with presence of both anxiety and depression (79, 80, 82, 95, 102). This type of analysis precludes our ability to observe the influence of anxiety alone, depression alone, and both anxiety and depression on PTB, consequently, limiting our understanding of the association between anxiety and depression with preterm birth.

Furthermore, anxiety and depression are correlated with socioeconomic status. Anxiety and depression are both more prevalent among women living in disadvantaged areas than in advantaged areas (80, 109-111). Anxious and depressed women living in less advantaged areas may interpret the deprivation associated stressors such as financial hardship, economic insecurity, and societal disadvantages as a threat (28). They also may not effectively cope with stressful situations due to the lack of resources they have (personal and social resilience or support factors available to help them cope with the stressful situations) (28). They are also less likely to access resources, such as, health services and cultural, recreational, and physical activities. Furthermore, they are less likely to have support and may be less able to manage or

cope with their stressors. Therefore, women exposed to social disadvantages are more likely to be severely emotionally distressed compared to those living in more advantaged areas (79, 95, 112, 113). Consequently, the risk of delivering preterm is more likely to be elevated in this group of women. Thus, it is hypothesized that the risk of PTB that is associated with anxiety and/or depression during pregnancy may differ by neighbourhood socioeconomic status. To our knowledge, this hypothesis has not been examined.

This doctoral research aimed to examine the association of the presence of anxiety symptoms alone, depression symptoms alone, and both anxiety and depression symptoms with PTB. This study further aimed to examine whether anxiety, depression, and the presence of both anxiety and depression interact with neighbourhood SES to increase the risk of PTB. A detailed description of the association between anxiety and depression and PTB may provide a deeper understanding about the risk factors for PTB. This may ultimately help identify the areas where resources (health, social, and economic resources) could be more effectively targeted to reduce the incidence of PTB.

Research Objective

General Research Objective

This doctoral research examined neighbourhood SES and maternal anxiety and depression during pregnancy as risk factors for PTB and the utility of existing anxiety scales in measuring anxiety in pregnancy.

Specific Research Objectives

This doctoral research addressed the following three specific research objectives:

1. To develop and internally validate a prediction model to examine the ability of neighbourhood level SES to predict PTB

2. To evaluate the performance of multiple anxiety scales in the same or comparable sample of pregnant women to elucidate the suitability and comparability of self-reported anxiety scales in measuring anxiety during pregnancy

3. To examine the association of anxiety symptoms alone, depression symptoms alone, and both anxiety and depression symptoms with PTB and further examine whether neighbourhood SES modifies this association.

Chapter 2: Data Harmonization

Introduction

Linking data from multiple cohort studies provides opportunities to increase the power of the study and to answer novel research questions that could not be addressed using a single study (114, 115). However, if individual datasets from different studies measured the same construct or variables differently, this poses challenges for data linkage. These challenges are addressed by data harmonization. Data harmonization refers to all the efforts that provide comparability of datasets from heterogeneous sources and allows for combining, pooling, or integrating them in a coherent way (116). Data harmonization can take a prospective or retrospective approach. Prospective data harmonization occurs at the initial stage of study design, or at least before data collection. For this, investigators agree on a common core set of variables or measures, compatible data collection tools, and standard operating procedures (116). Retrospective harmonization targets synthesis of information already collected by existing studies. For this, researchers define a core set of variables, assess the potential for creating a matching variable, and develop strategies for synchronization. Access to extensive documentation and conversations with research teams of existing studies allows researchers to understand each study's methodologies and data management systems (116).

Data Sources

This research combined existing datasets from the All Our Families (AOF) and the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort studies. The AOF cohort study recruited 3,341 pregnant women and the APrON cohort study recruited 2,187 pregnant women, with 231

women participating in both studies. Linkage of the existing data from the AOF and APrON cohort studies was justifiable (114), given the homogeneity between the methodologies and inferentially equivalent variables across these studies. Both studies were prospective pregnancy cohort studies, and were conducted in Calgary, Alberta. Additionally, these studies had similar recruitment time periods (2008-2012), inclusion criteria (such as maternal age and gestational weeks), cohort characteristics (such as age, income, and parity), sampling design (non-probability sampling), and data collection methods (self-administered questionnaire) (117, 118). Both studies have collected detailed data on demographics, socioeconomic status, lifestyle, social support, anxiety and depression, and preterm birth (117, 118), the variables necessary for this current research. However, each study had measured/recorded the same construct/variables (related to this current research) differently. Therefore, data harmonization strategies were used to generate a comparable dataset across studies.

Variable Harmonization

Variables related to this research were harmonized in each dataset considering multiple features of the data. These features included whether the variables were completely or partially identical regarding: (a) the construct measured; (b) question asked/responded; (c) the measurement scale used; (d) the frequency of measurement; (e) when in pregnancy the variable was measured, and (f) the coding of variables and responses. The coding features of variables and responses considered for data harmonization included variable name, type, format, and response categories, variable value label and definition, and missing values including response categories “not applicable”, “not stated”, and “don’t know” (114-116). If the

construct was not measured in one of the datasets or if different measurement scales were used to measure the same construct across the datasets, the variables were deemed completely un-matching. The variables deemed completely un-matched were not combined. However, no important variables had to be excluded from the present study due to this reason. If the variables were an exact match for each of these features, variables were considered completely matching and they were pooled as is. If the variables were same in terms of what construct was measured, but were different in terms of frequency of measurement, the gestational age at measurement, and variable response coding, these variables were considered partially matching. These partially matching variables were synchronized across the datasets considering the multiple features of data harmonization mentioned above.

Several variables such as ethnicity, income, parity, gestational age, anxiety, depression, and smoking were harmonized. To illustrate, one variable, maternal age was completely matching across the datasets, except the name of the variable and coding of missing values. In AOF, maternal age was asked using a statement “maternal age at recruitment” and in APrON, it was asked using a statement “maternal age at first contact visit”. In both datasets, response to maternal age was recorded as continuous data. However, in the AOF dataset, the missing value was recorded as “.” and in the APrON dataset, it was recorded as “999”. Accordingly, the variable name and missing values were recoded to synchronize the data across the datasets. Another variable, current marital status, was partially identical across the datasets as the construct measured (or question asked) was completely identical across both datasets but the variable response categories and the value level coding were different across both datasets. To

illustrate, in AOF, the marital status was asked using a question “how would you describe your current marital status?”. The responses were recorded as “single” (with a value label “1”), “single with partner” (with value label “2”), “married” (with a value label “3”), “common-law” (with a value label “4”), “divorced” (with a value label “5”), “separated” (with a value label “6”), and missing (with a value label “ .”). In APrON, a similar question “what is your current marital status?” was asked to measure marital status. Responses were recorded as “single” (with a value label “0”), “married” (with a value label “1”), “divorced” (with a value label “2”), “common-law” (with a value label “3”), “widowed” (with a value label “4”), “separated” (with a value label “5”), and “missing” (with a value label “999”). As the variable or response categories were collapsible to identical and meaningful categories across the datasets, the variable response was re-categorized/re-organized into 3 identical categories in both datasets (with identical value label coding) to optimize the utility of data from both datasets. Accordingly, the combined variable had response categories of “single” (with a value label “0”), “married/common-law” (with a value label “1”), and “divorced/separated/widowed” (with a value label “2”), with missing value labelled as “ .”.

If the variables were measured multiple times at different gestational ages, variables were synchronized using the gestational age at the time of each measurement. To illustrate, the AOF and APrON datasets both measured depression during pregnancy using the Edinburgh Postnatal Depression Scale (EPDS). However, the datasets were not compatible in terms of frequency of measurement and gestational age at each measurement. The AOF dataset measured depression at two times, first at <25 weeks of gestation and again between 34 and 36 weeks of

gestation. The data from the first and second measurements were recorded as two separate variables. However, the APrON dataset measured depression three times during pregnancy and the data were recorded as three separate variables: (a) the first measurement, which provided depression data in the first or second trimester for all women; (b) the second measurement, which provided depression data in the second trimester for only those women who were in their first trimester at the time of the first assessment; and (c) the third measurement, which provided depression data in the third trimester for those women who were in their first or second trimester at the time of first assessment. The data on depression were harmonized into three trimesters for both datasets, using the data on gestational age at the time of each measurement that was recorded in both datasets. Coding for each item of EPDS was also checked to make sure that both datasets had identical coding. Accordingly, the three synchronized variables for depression – "total depression score in the first trimester", "total depression score in the second trimester", and "total depression score in the third trimester" – in both datasets were combined into a single dataset. Each of these three variables were later dichotomized using a standard cut-off point, and their response categories were coded as "yes" (with a value label "1") and "no" (with a value label "0") or missing. Then, these three dichotomized variables were further converted into a single dichotomized variable, that is depression in any trimester. Responses categories for the variable (depression in any trimester) were coded as "yes" (with a value label "1") and "no" (with a value label "0").

If the datasets measured the same construct using different measurement scales, the variable harmonization and data pooling (of the variables measured by different scales) was not

justifiable. Instead, the overlapped sample who participated in both cohort studies were identified and the analysis of the construct was restricted to this sample. In particular, anxiety during pregnancy was measured in both datasets using different scales: the AOF dataset had anxiety data measured by the Edinburgh Postnatal Depression Scale anxiety subscale (EPDS-3A) and the State Trait Anxiety Inventory (STAI), whereas the APrON dataset had anxiety data measured by the EPDS-3A and the SCL-90 scale. Thus, the anxiety data measured by the two scales, the SCL-90 and the STAI, were not matching across these datasets. While it was not feasible to compare the anxiety data measured by these three anxiety scales in the full cohort, there were 231 women who participated in both datasets. We identified those participants from both datasets, linked their anxiety data measured in both datasets, and restricted our analysis to the overlapped sample to address the research objective. Furthermore, if the variables were important to answer the research question but they were available in one of the datasets, a sensitivity analysis was done in the dataset that measured those variables. For example, data on prenatal care and prior preterm birth were available in the AOF cohort dataset but were not available in the APrON cohort dataset. We developed a prediction model for preterm birth in a combined dataset including those variables that were available in both datasets. As prenatal care and prior preterm birth are known risk factors for preterm birth, a sensitivity analysis was also performed using the AOF dataset, whereby these two variables were added to the prediction model (that was developed in the combined dataset) to assess whether addition of these variables improves the performance of the prediction model.

The consistency of variables across two datasets in terms of variable name (e.g., smoking), variable label (smoking status before pregnancy), variable value label ("no" for 0, "yes" for 1), variable type (continuous or discrete), variable format (numeric or character), and missing value coding ("." or "999") was established. Cross-tabulation or five-number summary (as appropriate to the data type) for each harmonized variable was done in each dataset as a final check for harmonization. Finally, once the selected variables were harmonized in each dataset, the harmonized two datasets were then combined into a single dataset (n=5,588). Women who participated in both studies (n=231) were counted only once. This means 231 women's data in AOF was retained, but their data in APrON was deleted. However, for the analysis that was restricted to these 231 women, additional data measured by APrON was retained in the combined data (i.e., anxiety data measured using SCL-90 scale). Data harmonization procedures were documented and shared with the data holders (the AOF and the APrON research teams) to make sure that the data harmonization process maintained the integrity of the original data and the original data was not lost.

Overall, data harmonization is an important aspect of conducting research using multiple datasets. It generates comparable data across studies and facilitates for pooling relevant data across studies. Pooling data from different studies extends the utility of individual study as it provides an opportunity to increase sample size or the power of the study and answer research questions that could not be addressed in a single study. Additionally, it creates a collaborative research environment, minimizes the duplication of research, and increases research feasibility by allowing to conduct research at relatively rapid and low cost.

Chapter 3: Does Neighbourhood Socioeconomic Status Predict the Risk of Preterm Birth? A Community-based Canadian Cohort Study

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Abstract

Objective

This study developed and internally validated a predictive model for preterm birth (PTB) to examine the ability of neighbourhood socioeconomic status (SES) to predict PTB.

Design

Cohort study using individual-level data from two community-based prospective pregnancy cohort studies (All Our Families (AOF) and Alberta Pregnancy Outcomes and Nutrition (APrON)) and neighbourhood SES data from the 2011 Canadian census.

Setting

Calgary, Alberta, Canada

Participants

Pregnant women who were <24 weeks of gestation and >15 years old were enrolled in the cohort studies between 2008-2012. Overall, 5,297 women participated in at least one of these cohorts: 3,341 women participated in the AOF study, 2,187 women participated in the APrON study, and 231 women participated in both studies. Women who participated in both studies were only counted once.

Primary and Secondary Outcome Measures

Preterm birth (delivery prior to 37 weeks of gestation)

Results

The rates of PTB in the least and most deprived neighbourhoods were 7.54% and 10.64%, respectively. Neighbourhood variation in PTB was 0.20, with an intra-class correlation of 5.72%. Neighbourhood SES, combined with individual level predictors, predicted PTB with an area under the receiver operating characteristic curve (AUC) of 0.75. The sensitivity was 91.80% at a low risk threshold, with a high false positive rate (71.50%), and the sensitivity was 5.70% at a highest risk threshold, with a low false positive rate (0.90%). An agreement between the predicted and observed PTB demonstrated modest model calibration. Individual level predictors alone predicted PTB with an AUC of 0.60.

Conclusions

Although neighbourhood SES combined with individual level predictors improved overall prediction of PTB compared to individual level predictors alone, the detection rate was insufficient for application in clinical or public health practice. A prediction model with better predictive ability is required to effectively find women at high risk of preterm delivery.

Introduction

Globally, 11.1% of births are preterm (6). Preterm birth (PTB), delivery prior to 37 weeks of gestation, is a major contributing factor to neonatal deaths (1, 3), and amongst survivors, PTB is also a significant risk factor for short- and long-term morbidity (2-4). The incidence of PTB and its associated mortality and morbidity could potentially be reduced if women at risk of delivering preterm were identified early in gestation and appropriately managed (119, 120). The etiology of PTB is multifactorial (11, 16, 20), and one risk factor for PTB may be neighbourhood socioeconomic status (SES) (16, 24, 27): the rate of PTB in low SES neighbourhoods is higher than the rate in high SES neighbourhoods (32, 33, 35). Neighbourhood SES is an area level measure of SES, which aggregates individual SES (such as income, education, and employment status) at a certain geographical level (24). The high rate of PTB in low SES neighbourhoods is not only related to the fact that women living in these neighbourhoods have higher individual-level risk factors for PTB. Neighbourhoods themselves can also increase the risk of PTB by exposing individuals to elevated risk (22, 24, 27). Low SES neighbourhoods influence an individual's ability to fulfill daily needs, access resources, make lifestyle choices, and cope with different situations (22, 24, 27). Accordingly, women living in low SES neighbourhoods have less access to healthy foods, quality health services, opportunities for leisure activity, and social support, and have more exposure to societal stressors, crimes, and poor air and water quality. All of these neighbourhood level factors can increase the risk of PTB among women living in these neighbourhoods through material, psychosocial, behavioral, and biological mechanisms (22, 24, 27, 28).

While many studies have examined the association between neighbourhood SES and PTB (32, 33, 35), our understanding about the ability of neighbourhood SES to predict the risk of PTB is limited. It is possible that even strongly associated risk factors can have a low capacity to discriminate PTB in the population (45-47). Similarly, a statistically significant association between neighbourhood SES and PTB may exist, with small/no variation of PTB at neighbourhood level (49-51). Thus, the association may provide unreliable information about the likelihood of delivering preterm infants among women living in certain neighbourhoods and may mislead decision-makers in implementing public health interventions targeted at specific areas (49, 50). As previous studies have not developed and validated a prediction model for PTB to evaluate the predictive ability of neighbourhood SES, information about the ability of neighbourhood SES to predict PTB is lacking.

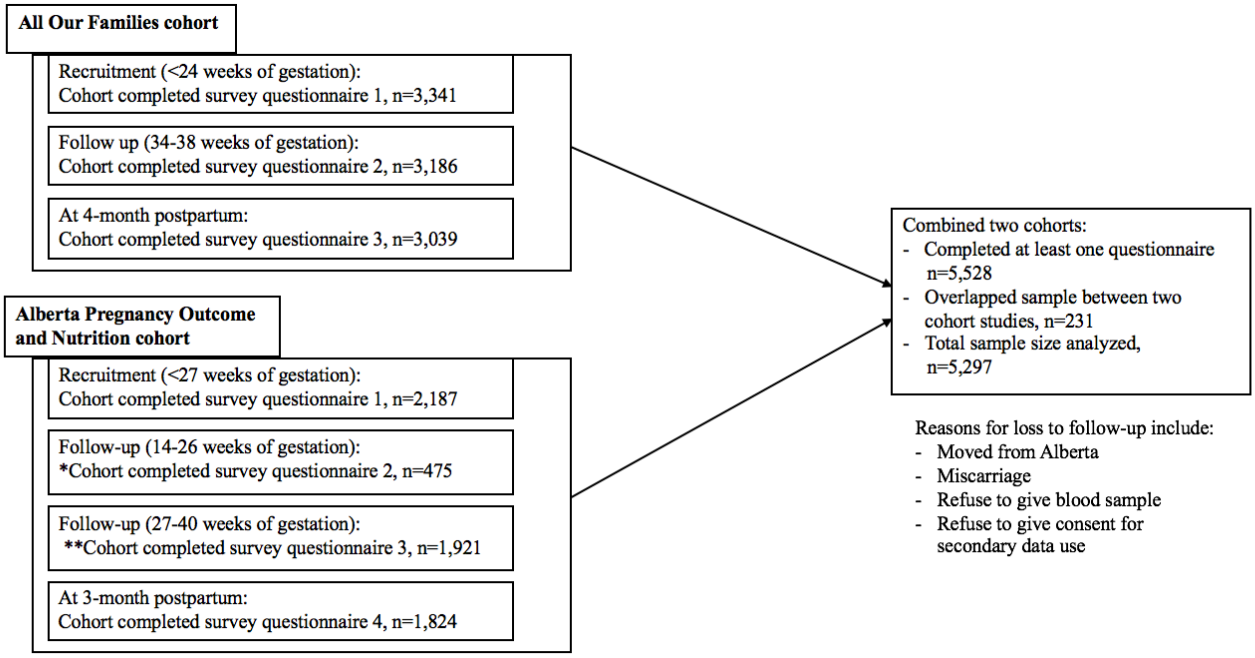
A better understanding of the ability of neighbourhood SES to predict PTB has its own importance as it may improve our capacity to accurately discriminate between women at high and low risk for delivering preterm infants (44, 45). The accurate discrimination capacity may offer a more valid prediction about the future probability of delivering a preterm infant in an individual woman coming from certain neighbourhoods (44, 45). The use of valid prediction models may help us effectively identify women at high risk of delivering preterm infants, and in planning suitable public health interventions targeting women from low SES neighbourhoods, such as appropriate triage of women into low and high risk prenatal care. This is timely and relevant given that individual level risk factors (including biomarkers) have shown a low discriminatory accuracy in predicting PTB (46, 47), resulting in ineffective early identification of

women at risk for delivering preterm infants. Therefore, this study developed and internally validated a predictive model to examine the ability of neighbourhood SES to predict PTB.

Methods

Data Sources

This study combined existing datasets from two community-based prospective pregnancy cohort studies in Alberta, Canada: All Our Families (AOF: n=3,341) and Alberta Pregnancy Outcome and Nutrition (APrON: n=2,187)) (Figure 1). The description and comparability of these two cohort studies is available elsewhere (117, 118) and justifies combining these data sources (114). Briefly, each cohort study had similar recruitment periods (2008-2012), inclusion criteria, sampling design, and data-collection methods (117, 118). Both studies collected data on socio-demographics, lifestyle, social support, depression, and PTB (117)– the core individual-level variables necessary for this research.



*Participants who were 0-13 weeks of gestation during the recruitment were eligible to fill out the questionnaire 2. ** Participants who were 0-26 weeks of gestation during recruitment were eligible to fill out the questionnaire 3.

Figure 1: Flowchart of Study Cohort

We obtained two de-identified cohort datasets linked with neighbourhood SES data from SAGE (Secondary Analysis to Generate Evidence), the secure data repository developed by PolicyWise for Children & Families, which houses these datasets. Neighbourhood SES data were measured by the median personal income and the Pampalon material deprivation index (both measures were derived from 2011 Statistics Canada census) (25, 121), which were both aggregated at the dissemination area (DA) level. DA is the smallest geographic unit available in the Canadian census, consisting of 400-700 persons (26). The Pampalon material deprivation index is a composite measure of neighbourhood SES that combines the proportion of persons without high school diplomas (education), the average personal income (income), and the rate of

unemployment (employment) within the DA (25). Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary.

Patient and Public Involvement

This study used de-identified secondary data. Patients and public were not involved in this study.

Data Harmonization and Combination

Individual level variables in the two studies were harmonized in each dataset considering multiple factors. These factors included whether the variables were completely or partially identical regarding question asked/responded, the response coded (value level, value definition, data type), the frequency of measurement, the pregnancy time-point of measurement, and missing values. If the variables were an exact match for each of these factors, they were pooled as is. If the variables were partially matched, data harmonization was performed considering these multiple factors. The variables deemed completely un-matched were not combined; thus, they were not included in this study. However, no important variables had to be excluded from the study due to this reason. Once the selected variables were harmonized in each dataset, the two datasets were appended into a single new dataset. Women who participated in both studies (n=231) were counted only once.

The harmonized variables included maternal age, marital status, ethnicity, duration of stay in Canada, body mass index, parity, education, household income, depression during pregnancy,

and smoking, alcohol consumption, and drug abuse before the pregnancy. Deliveries that occurred before the completion of 37 weeks of gestation were considered as preterm births.

Data Analysis

Univariate analysis was performed to observe the distribution of each variable. Bivariate analyses using chi-square tests were performed to identify individual level variables associated with PTB ($p<0.25$). Multivariable conventional logistic regression models, followed by multilevel logistic regression models, as outlined by Merlo et al 2016 (51), were developed using bootstrapped samples with 1000 replications (training dataset) (Appendix 4). Missing data were deleted using variable wise or pair wise deletion approach for bivariate analysis, followed by the listwise deletion approach for regression models. All analyses were performed using STATA/IC software – version 14.1.

Model validation and model performance assessment

The bootstrap procedure was employed for internal validation of the model (45, 48). Model performance was evaluated in the original sample (validation dataset) using measures of model calibration (the correspondence between predicted and observed outcome rates), risk stratification capacity (proportion of women categorized as low vs high risk, or the distribution of the women in each predicted risk category), and classification performance or discrimination accuracy (true positive and false positive rates, positive and negative predictive values, positive and negative likelihood ratios, and area under the receiver operating characteristic curve (AUC)). To obtain these measures, the predicted probability of PTB for each woman was

estimated and was categorized into four risk groups (<5%, ≥5 - 10%, ≥10 - 15%, and ≥15%). The difference in AUC estimates between the bootstrapped sample and the original sample was assessed as described by optimism (45, 48). Data on prenatal care and previous PTB were not available in APrON cohort dataset. A sensitivity analysis was performed using only the AOF dataset, whereby two variables, previous PTB and total number of prenatal care visits, were added to the final models (conventional logistic regression model and multilevel random effect model) to assess whether addition of these variables improved model performance.

Results

The total sample size from the combined cohort was 5,297. The proportion of missing data ranged from 1.52% for depression to 7.51% for gestational age at delivery. The majority of women were under the age of 35 years, were married or living with a common-law partner, were Caucasian, and approximately half of the women were primiparous. Almost three quarters of women had completed more than high school education and had a household income ≥$70,000, while approximately one quarter of women were living in the least deprived neighbourhood (Table 1). Overall, 7.26% (95% CI=6.57, 8.07) of women delivered preterm infants, with 7.54% among women living in the least deprived neighbourhoods and 10.64% among women living in the most deprived neighbourhoods. Compared to women who delivered at term, a higher proportion of women who delivered preterm infants were primiparous, non-white, obese, and were living in the most deprived neighbourhood (Table 1).

Table 1: Distribution of Maternal Characteristics across Preterm Birth Status[a]

Variables	Overall (n=5297)		Preterm Birth (Gestational Age <37 weeks) n=356		Term Birth (Gestational Age ≥37 weeks) n=4546		χ^2 p-value
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
Maternal age							0.332
<35yrs	4117 (79.23)	78.10, 80.31	269 (77.08)	72.36, 81.19	3541 (79.27)	78.05, 80.43	
≥35yrs	1079 (20.77)	19.68, 21.89	80 (22.92)	18.80, 27.63	926 (20.73)	18.80, 27.63	
Marital status							0.657
Single/divorced/separated	262 (5.06)	4.49, 5.69	17 (4.96)	3.10, 7.83	198 (4.44)	3.87, 5.09	
Married/common-law	4916 (94.94)	94.30, 95.50	326 (95.04)	92.17, 96.89	4260 (95.56)	94.91, 96.13	
Ethnicity							0.004
White/Caucasian	4085 (78.98)	77.85, 80.07	253 (73.76)	68.83, 78.15	3574 (80.28)	79.08, 81.42	
Others	1087 (21.02)	19.93, 22.15	90 (26.24)	21.85, 31.16	878 (19.72)	18.58, 20.92	
Duration of stay in Canada							0.061
<5 years	473 (9.26)	8.49, 10.08	39 (11.64)	8.61, 15.54	380 (8.63)	7.84, 9.25	
Born/5 years+	4636 (90.74)	89.91, 91.51	296 (88.36)	84.45, 91.38	4022 (91.37)	90.50, 92.16	
Body mass index							0.001
Underweight (<18.5kg/m2)	214 (4.33)	3.80, 4.94	12 (3.69)	2.10, 6.39	180 (4.23)	3.66, 4.87	
Normal weight (18.5 - 24.99)	3084 (62.45)	61.09, 63.79	183 (56.31)	50.85, 61.62	2694 (63.28)	61.82, 64.72	
Overweight (25 - 29.99 kg/m2)	1066 (21.59)	20.46, 22.76	72 (22.15)	17.69, 27.00	924 (21.71)	20.49, 22.97	
Obesity (≥30 kg/m2)	574 (11.62)	10.76, 12.54	58 (17.85)	14.05, 22.40	459 (10.78)	9.88, 11.75	
Parity							0.004
Primiparous	2649 (51.27)	49.90, 52.63	201 (58.94)	54.64, 64.80	2266 (50.92)	49.45, 52.39	
Multiparous	2518 (48.73)	47.37, 50.09	140 (41.06)	35.19, 45.36	2184 (49.08)	47.61, 50.54	
Intended pregnancy	4175 (80.51)	79.40, 81.56	282 (81.98)	77.54, 85.69	3633 (81.42)	80.25, 8253	0.805
Smoked before pregnancy	1095 (21.13)	20.04, 22.26	85 (24.71)	20.43, 29.55	913 (20.47)	19.31, 21.68	0.062
Alcohol consumption before pregnancy	4363 (84.13)	83.11, 85.10	295 (85.76)	81.64, 89.07	3770 (84.49)	83.39, 85.52	0.531
Drug abuse before pregnancy	750 (14.48)	13.54, 15.46	54 (15.70)	12.22, 19.94	643 (14.43)	13.42, 15.49	0.519

Variables	Overall (n=5297)		Preterm Birth (Gestational Age <37 weeks) n=356		Term Birth (Gestational Age ≥37 weeks) n=4546		$\chi 2$ p-value
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
Maternal education							0.917
Less than high school	174 (3.37)	2.91, 3.90	11 (3.22)	1.79, 5.72	126 (2.84)	2.39, 3.37	
Completed high school	893 (17.31)	16.29, 18.36	56 (16.37)	12.81, 20.69	722 (16.25)	15.19, 17.36	
More than high school	4093 (79.32)	78.19, 80.40	275 (80.41)	75.85, 84.28	3595 (80.91)	79.73, 82.04	
Household income							0.436
≥$100,000	2659 (52.52)	51.14, 53.89	176 (52.54)	47.17, 57.84	2358 (53.98)	52.50, 55.45	
$70,000 - <$100,000	1204 (23.78)	22.63, 24.97	74 (22.09)	17.96, 26.86	1059 (24.24)	22.99, 25.53	
$40,000 - <$70,000	723 (14.28)	13.34, 15.27	51 (15.22)	11.75, 19.49	591 (13.53)	12.55, 14.57	
<$40,000	477 (9.42)	8.64, 10.25	34 (10.15)	7.33, 13.88	360 (8.24)	7.46, 9.09	
Inadequate social support anytime during pregnancy	1148 (22.07)	20.96, 23.22	84 (24.21)	19.98, 29.00	955 (21.37)	20.19, 22.59	0.216
Presence of depression anytime during pregnancy	1311 (25.14)	23.98, 26.33	96 (27.67)	23.20, 32.61	1086 (24.21)	22.97, 25.48	0.149
Neighbourhood deprivation index							0.002
Quintile 1 (least deprived)	1323 (27.08)	25.85, 28.35	93 (26.12)	21.81, 30.94	1176 (27.68)	26.36, 29.05	
Quintile 2	1259 (25.77)	24.56, 27.01	76 (21.35)	17.39, 25.92	1119 (26.34)	25.04, 27.69	
Quintile 3	972 (19.90)	18.80, 21.04	71 (19.94)	16.10, 24.43	839 (19.75)	18.58, 20.97	
Quintile 4	736 (15.07)	14.09, 16.09	52 (14.61)	11.30, 18.67	639 (15.04)	13.99, 16.15	
Quintile 5 (most deprived)	595 (12.18)	11.29, 13.14	64 (17.98)	14.32, 22.32	475 (11.18)	10.27, 12.16	
Neighbourhood median personal income							0.054
Quintile 1 (least deprived)	1549 (31.05)	29.78, 32.35	106 (29.78)	25.24, 34.74	1369 (31.49)	30.12, 32.89	
Quintile 2	1403 (28.13)	26.89, 29.39	96 (26.97)	22.60, 31.82	1229 (28.27)	26.95, 29.63	
Quintile 3	881 (17.66)	16.62, 18.74	57 (16.01)	12.55, 20.20	776 (17.85)	16.74, 19.01	
Quintile 4	666 (13.35)	12.43, 14.32	47 (13.20)	10.06, 17.14	574 (13.20)	12.22, 14.24	
Quintile 5 (most deprived)	489 (9.80)	9.00, 10.66	50 (14.04)	10.80, 18.06	399 (9.18)	8.35, 10.07	

[a]sample size between variables differs as missing values were deleted using variable wise or pair wise deletion approach

As shown in Table 2, a conventional logistic regression model that included individual level predictors (parity, ethnicity, body mass index, smoking, depression, and household income) showed an AUC of 0.60 (95% CI=0.56, 0.63). The multilevel model that included individual level predictors, and a random effect at the neighbourhood level showed large variation in PTB at the neighbourhood level (neighbourhood variance=0.20, intracluster correlation (ICC)=5.72%, median odds ratio (MOR)=1.53), with an AUC of 0.75 (95% CI=0.73, 0.78). After inclusion of neighbourhood SES (deprivation index) in the multilevel model, although deprivation index was not significantly associated with PTB (OR=1.19, 95% CI=0.78, 1.79), neighbourhood variance decreased to 0.15, the ICC to 4.45%, and the MOR to 1.46, with an AUC of 0.75 (95% CI=0.73, 0.78). The MOR of 1.46 for PTB indicates that in the median case, the residual heterogeneity between neighbourhoods increased by 1.46 times the individual odds of PTB when randomly picking out two persons in different neighbourhoods. Furthermore, the multilevel model that contained median personal income, as a measure of neighbourhood SES, showed similar variance as the model that contained deprivation index.

Table 2: Predictive Models for Preterm Birth[a]

	Model 1[b] OR (95% CI)	**Model 2[c] OR (95% CI)**	**Model 3[d] OR (95% CI)**
Ethnicity			
White/Caucasian (ref)	-	-	-
Non-white	1.50 (1.11, 2.04)	1.48 (1.11, 1.96)	1.49 (1.13, 1.99)
Parity			
Multiparous (ref)	-	-	-
Primiparous	1.49 (1.21, 1.84)	1.52 (1.19, 1.93)	1.53 (1.20, 1.95)
Body mass index			
Normal weight (ref)	-	-	-
Underweight	0.99 (0.46, 2.10)	1.01 (0.47, 1.14)	1.00 (0.35, 2.83)
Overweight	1.18 (0.88, 1.57)	1.14 (0.76, 1.68)	1.13 (0.72, 1.78)
Obesity	1.94 (1.41, 2.65)	1.95 (1.25, 3.04)	1.95 (1.16, 3.30)
Smoked before pregnancy			
No (ref)	-	-	-
Yes	1.20 (0.90, 1.60)	1.19 (0.78, 1.79)	1.19 (0.77, 1.82)
Depression during pregnancy			
No (ref)	-	-	-
Yes	1.10 (0.84, 1.46)	1.12 (0.76, 1.66)	1.13 (0.74, 1.71)
Household income			
≥$100,000 (ref)	-	-	-
$70,000 - <$100,000	0.82 (0.61, 1.12)	0.82 (0.51, 1.33)	0.84 (0.55, 1.28)
$40,000 - <$70,000	0.75 (0.70, 1.31)	0.96 (0.57, 1.62)	0.99 (0.58, 1.69)
<$40,000	0.92 (0.71, 1.66)	1.05 (0.60, 1.81)	1.10 (0.63, 1.88)
Neighbourhood SES	-		
Q1 least deprived (ref)		-	-
Q2		0.86 (0.53, 1.39)	0.97 (0.64, 1.49)
Q3		0.96 (0.58, 1.59)	0.87 (0.52, 1.47)
Q4		0.99 (0.60, 1.58)	0.90 (0.51, 1.59)
Q5 most deprived		1.20 (0.63, 1.85)	1.01 (0.55, 1.86)
Neighbourhood level variance	-	0.15 (0.03, 0.89)	0.14 (0.03, 0.88)
ICC (%)[e]	-	4.45 (0.07, 23.25)	4.27 (0.06, 23.59)
MOR	-	1.46	1.44
Proportion of neighbourhood level variance explained by neighbourhood SES (%)	-	25.00	25.16
AUC	0.60 (0.56, 0.63)	0.75 (0.73, 0.78)	0.75 (0.72, 0.77)

[a]prediction models were developed in bootstrapped samples with 1000 replications; [b]conventional logistic regression model that includes individual level predictors; [c]multilevel logistic regression model that includes random intercept at neighbourhood level, neighbourhood deprivation index, and all the individual level predictors contained in the logistic

regression model; [d]multilevel logistic regression model that includes random intercept at neighbourhood level, neighbourhood median personal income, and all the individual level predictors contained in the logistic regression model; [e]ICC calculation follows standard logistic distribution with variance π2/3 for the level 1, where π denotes the mathematical constant 3.1416; MOR: median odds ratio; ICC: intra-cluster correlation; AUC: area under the receiver operating characteristic curve

Predicted probabilities of PTB in the multilevel model that contained individual level predictors and deprivation index ranged from 2.77% - 27.00%. Calibration of the model predicting PTB was adequate, as shown by an agreement between the model-predicted probability for PTB and the proportion of observed PTB, particularly for low risk categories. Specifically, the observed PTB rate within the predicted risk category of ≥5% - 10% was 7.30%, which falls within the risk category range; the same was true for the risk category of <5%. The risk-stratification capacity of the model was adequate – it assigned women to the different risk categories for PTB, where almost 90% of women were assigned to the low risk categories (Table 3).

Table 3: Performance of Predictive Models for Preterm Birth (n=4,357)[a]

Predictive models	Model calibration		Risk stratification capacity n (%)	Model discrimination[b]						
	Predicted probability of PTB (%)	Observed PTB n (%) 95% CI		Sensitivity (%)	Specificity (%)	Classification accuracy (%)	PPV (%)	NPV (%)	LR+ (%)	LR- (%)
Conventional logistic regression model with individual level predictors, i.e., parity, ethnicity, body mass index, smoking, depression, and household income	<5	42 (4.81) 3.43, 6.03	873 (20.04)	-	-	-	-		-	-
	≥5 – 10	197 (6.96) 6.02, 7.81	2832 (65.00)	85.76	22.43	26.54	7.66	95.44	1.10	0.63
	≥10 – 15	77 (12.56) 9.99, 15.96	613 (14.07)	20.12	89.42	84.58	12.43	93.70	1.90	0.89
	≥15	4 (10.26) 2.82, 24.37	39 (0.90)	1.55	99.14	92.31	8.82	93.03	1.80	0.99
Multilevel logistic regression model with neighbourhood deprivation index and individual level predictors	<5	26 (2.22) 1.50, 3.22	1177 (27.01)	-	-	-	-	-	-	-
	≥5 – 10	197 (7.30) 6.40, 8.37	2690 (61.74)	91.80	28.50	33.09	9.12	97.80	1.28	0.29
	≥10 – 15	75 (17.24) 13.97, 21.09	435 (9.98)	29.40	90.20	85.83	19.00	94.20	3.00	0.78
	≥15	18 (32.73) 21.60, 46.20	55 (1.26)	5.70	99.10	92.30	32.80	93.10	6.22	0.95
Multilevel logistic regression model with neighbourhood median personal income and individual level predictors	<5	31 (2.64) 1.86, 3.73	1174 (26.97)	-	-	-	-	-	-	-
	≥5 – 10	192 (7.16) 6.24, 8.19	2683 (61.58)	90.30	28.30	33.13	8.95	97.40	1.26	0.34
	≥10 – 15	81 (18.08) 14.78, 21.92	448 (10.28)	29.40	89.90	85.85	18.60	94.20	2.92	0.78
	≥15	12 (23.08) 13.52, 36.53	52 (1.19)	3.80	99.00	92.20	23.10	92.10	3.84	0.97

[a]model performance was assessed in the original sample (study sample); [b]model discriminatory was calculated using cumulative row values as different cut-offs to define high risk, for example, if all women with a model predicted probability of a preterm birth of 5% or higher are considered to have a positive test, model with deprivation index and individual level predictors would have a sensitivity of 91.80% and specificity of 28.50%.
PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio

The classification accuracy of the model ranged from 33.09% to 92.30% in the different predicted risk categories: the proportion of women with preterm delivery who were identified as high risk for PTB (sensitivity) ranged from 5.70% to 91.80% and the proportion of women without preterm delivery who are identified as low risk (specificity) ranged from 28.50 to 99.10. The positive and negative likelihood ratios of the model for the highest predicted risk category for PTB were 6.22 and 0.95, respectively. The difference in the AUCs between the bootstrap sample (AUC=0.75, 95% CI=0.73, 0.78) and original sample (AUC=0.75, 95% CI=0.73, 0.78) was negligible (i.e., optimism=0.0001). While the multilevel model that contained median personal income showed similar model performance as the model that contained the deprivation index (except for sensitivity and positive predictive values for the highest risk category), the logistic regression model that included individual level variables showed lower model performance (Table 3 and Figure 2). In the sensitivity analysis, the addition of variables related to prenatal care visits and previous PTB did not change the model performance. The AUC increased by 2.00% for the conventional logistic regression model, but did not increase for the multilevel random effect model that contained the neighbourhood SES variable.

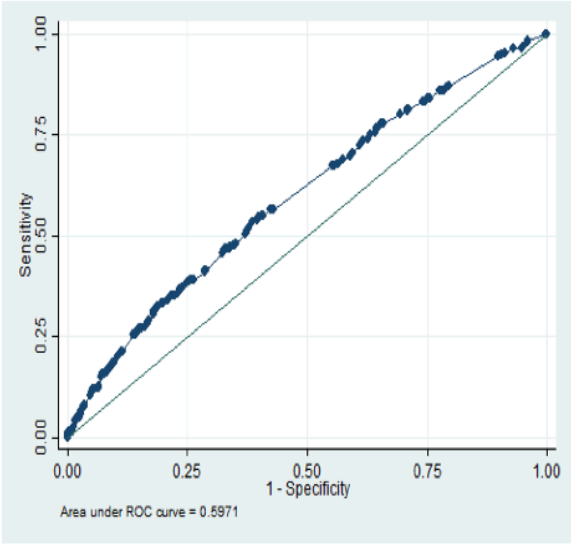


Figure 2a

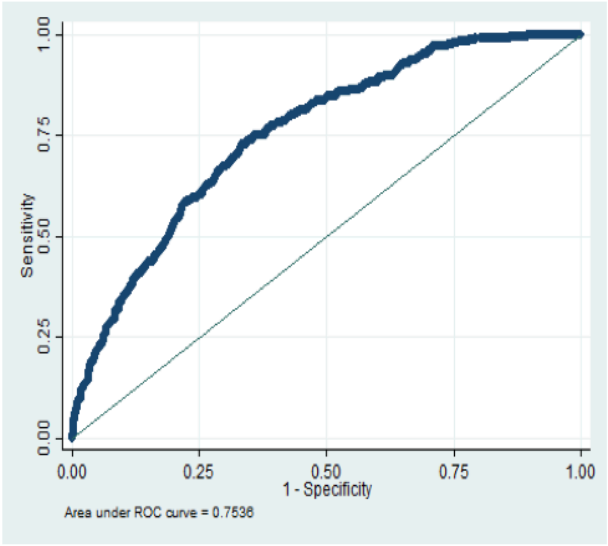


Figure 2b

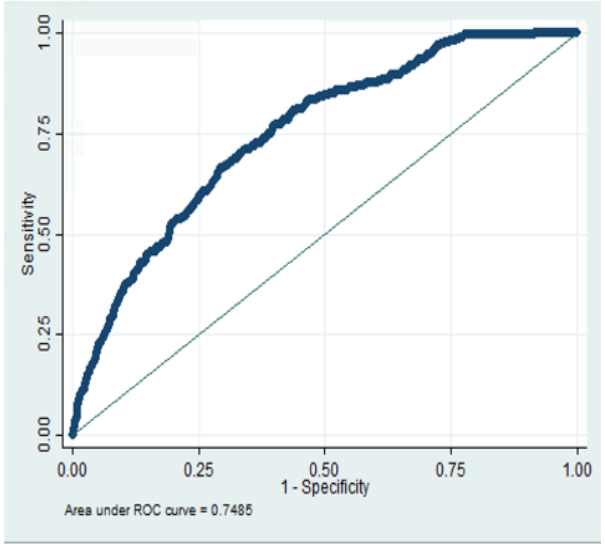


Figure 2c

[a] receiver operating characteristic curves of models were assessed in the original sample (study sample); predictors in Figure 2a included individual level variables, i.e., parity, ethnicity, body mass index, smoking, depression, and household income; predictors in Figure 2b included neighbourhood deprivation index and individual level variables; predictors in Figure 2c included neighbourhood median personal income and individual level variables.

Figure 2: Receiver Operating Characteristic Curves of Models Predicting Preterm Birth[a]

Discussion

Main Findings

This study developed and internally validated a prediction model to examine the ability of neighbourhood SES to predict the risk of PTB. This study found that approximately 6% of the total variance in PTB was attributable to neighbourhood circumstances (ICC=5.72%), and neighbourhood SES explained one quarter of the neighbourhood level variation in PTB. Neighbourhood SES combined with individual level predictors (parity, ethnicity, body mass index, smoking, depression, and household income) predicted the risk of delivering a preterm infant with an AUC of 0.75. The sensitivity was 91.80% at a lowest risk threshold, with a cost of high false positive (71.50%), and the sensitivity was 5.70% at a highest risk threshold, with a low false positive (0.90%). Neighbourhood SES combined with individual level predictors had a good risk-stratification and a modest calibration ability for identifying woman at risk for delivering a preterm infant.

Interpretation

Model discrimination (measured by AUC) was improved substantially when we combined individual level predictors with neighbourhood level information. While it has been previously demonstrated that individual level predictors including maternal characteristics, clinical risk factors, and biomarkers have low discriminatory accuracy in predicting the risk of PTB (AUC ranged from 0.60 to 0.67) (46, 47), this study enhances our understanding that adding neighbourhood level information can improve the discriminatory accuracy of PTB. Furthermore, it is important to note that a multilevel model that included a random effect for neighbourhood

and individual level information gives the maximum AUC that can be obtained by combining available individual level information and the neighbourhood identity (51). Neighbourhood identity captures the totality of potentially observable and unobservable neighbourhood factors (51, 122, 123).

As suggested by the classification performance of the model including neighbourhood SES and individual level predictors, a large proportion of women who were identified as high risk actually did not deliver preterm. Positive predictive value was improved, but still too low, as the predicted risk threshold increased, which was related to the high proportion of PTB in the threshold. The model had low sensitivity (5.70%) at the highest risk threshold, with a low false positive rate (0.90%). This means that a substantial number of women who were at high risk for delivering PTB would be identified as low risk (124). The LR positive test was improved (up to 6.22) for the highest risk threshold; however, this group only includes <6% of all women who actually delivered preterm. This dichotomy between improved LR and poor detection rates has also been noted previously (125).

While the prediction of PTB risk using neighbourhood SES is suboptimal, other commonly recognized risk factors for PTB also failed to sufficiently predict PTB. For example, it has been noted that a history of prior PTB has an LR+ of 3.24, short cervical length has an LR+ of 2.00, and vaginal fetal fibronectin has an LR+ of 3 in predicting PTB (126). Similarly, for a fixed false positive rate of 10%, maternal characteristics and obstetrical history have a sensitivity of 27.5% for PTB with an AUC of 0.61 (47). The less optimal predictive performance for identifying the

risk of PTB may be related to the complex underlying etiology of PTB, and a combination of multiple aspects of predictors (such as biomarkers, clinical risk factors, socio-demographics, and health behaviors) may be required to adequately predict such an outcome (125, 127). Our study further shows that inclusion of neighbourhood SES along with multiple individual level predictors would further improve the prediction of PTB. Altogether, it implies that identification of women at risk for delivering preterm infants should rely on multiple factors, and even women identified as low risk for PTB may need further monitoring/assessment and high quality prenatal care should be universal.

Our findings on neighbourhood variation and clustering of PTB suggest that pregnant women from the same neighbourhoods are more similar to each other than to women from different neighbourhoods with respect to the risk of PTB, and that some portion of this variation is related to neighbourhood SES. Overall, this finding reflects the presence of health disparities in PTB between neighbourhoods in Alberta, and justifies the relevance of including neighbourhood SES and neighbourhood targeted interventions. Furthermore, the share of the variance in PTB that are explained by neighbourhood level variance (as measured by ICC) offers understanding about the discriminatory accuracy as it corresponds to the AUC (51) – when the ICC is high the AUC is also high (51). However, previous research has emphasized identifying neighbourhood level risk factors associated with PTB or causal effects, which is difficult to establish due to the potential challenges. These challenges include reverse causation between neighbourhood circumstances and health, unmeasured confounding, residential mobility, possibility of the same individual variable being confounder and mediator, and changes in

neighbourhood context over the life process (24, 27, 128). Thus, a study aiming to establish a causal association demands longitudinal study design with repeated measurement of neighbourhood characteristics and outcomes over time in life-course processes (24, 27, 128).

Strengths and Limitations

To our knowledge, our study is the first to develop and internally validate a predication model for PTB to investigate the ability of neighbourhood SES to predict the risk of PTB, in contrast to the previous studies that examined mostly the association between neighbourhood SES and PTB. Our finding allows us to understand the relevance of area of residence (in general), and more specifically area level SES, in predicting the risk of maternal health outcomes. Our study used the simplest multilevel structure with individual and neighbourhood level predictors of PTB, data which can be easily collected in both community and clinical settings.

Our findings should be interpreted with a consideration of the limitations of our study. We were not able to separate-out spontaneous and iatrogenic PTB in the model due to data limitations – the predictive performance might be improved with a focus on spontaneous PTB. Our sample over-represents women from urban areas of Alberta, with high SES (57, 118, 129), thus limiting the generalizability of the findings to urban settings. The observed predictive ability of neighbourhood SES would have been underestimated as the relevance of neighbourhood SES status might be higher for those with low SES. Although the observed small difference in discriminatory accuracy between the bootstrapped sample and the original sample provided us with confidence about the reproducibility of our prediction model, as the

model was internally validated, it possibly showed artificially high performance; thus, model validation should be confirmed against external data. Use of area-based variables, where women living in the same area share the same value for the variable, can be a methodological problem. Outcomes could be affected by what geographical level or unit we choose to define area in the study. Individuals who live in the same area may also experience different contextual influences from many other areal units, and the timing and duration in which individuals experienced these contextual influences is also uncertain. Thus, it is hard to interpret neighbourhood influences on outcomes, including the performance of the model that contains a neighbourhood level variable. However, we defined neighbourhoods using the smallest geographic area (i.e., dissemination area), where people living in the smallest area are more likely to be similar for the outcomes, and used multilevel analysis that accounts for area level variation, an appropriate analytical approach for multilevel data.

Conclusions

Although the predictive performance of the model that contained neighbourhood SES and individual level predictors was better compared to the performance of individual level predictors alone, the performance was too low to consider its application in clinical or public health practices. While the development and validation of our predictive model is an important first-step towards the early identification of women at high risk for PTB based on neighbourhood risk assessment, a clinically-relevant validated model to predict the risk of PTB is yet to be identified. Future studies could develop a prediction model for PTB considering other clinically relevant individual and neighbourhood level predictors, separating out

spontaneous and iatrogenic PTB in the model, and externally validating their results to optimize the prediction and to improve its usefulness. The application of clinically useful prediction model would support healthcare providers and public health practitioners to make informed decisions on their care by improving their ability to identify woman most at risk of delivering preterm. As such, community level interventions combined with an individual-centered approach that attempts to change neighbourhood circumstances (health promoting or damaging features of neighbourhood including SES) and population characteristics (with focus to modifiable predictors) may be effective in reducing the incidence of PTB.

Chapter 4: Assessment of Anxiety during Pregnancy using Multiple Anxiety Scales: Do Anxiety Scales Differ in Their Ability to Assess Anxiety during Pregnancy?

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Abstract

Background

Information about the utility of anxiety scales in measuring anxiety during pregnancy is limited. This study examined the performance of multiple scales in measuring anxiety during pregnancy.

Methods

Anxiety data, measured by the State-Trait Anxiety Inventory-State (STAI-S) 20-item and 6-item scales, the Edinburgh Postnatal Depression Scale-Anxiety Subscale (EPDS-3A), and the Symptoms Checklist-90-Anxiety Subscale (SCL-90), were obtained from two pregnancy cohort studies in Alberta, Canada. Both cohorts completed the EPDS-3A, while a cohort involving 3,341 women completed the STAI-S and a cohort involving 2,187 women completed the SCL-90, with 231 women participating in both cohorts (overlapping sample). Confirmatory factor analysis was used to test the goodness-of-fit and Spearman correlation was used to estimate the correlation between the anxiety scores in the full sample (separately in each cohort) and the overlapping sample.

Results

The STAI-6 had adequate model fit, while the STAI-20 and the SCL-90 had inadequate model fit. Model fitness for the EPDS-3A could not be assessed due to its low number of items. The correlation between the STAI-20 and STAI-6 was excellent (r=0.93). The correlation of EPDS-3A with other anxiety scales was low to moderate (r (STAI-20)=0.57, r (STAI-6)=0.53, and r (SCL-90)=0.44). The correlation of SCL-90 with both the STAI-20 and the STAI-6 was low (r<0.50).

Limitations

This study cannot inform the clinical utility of the scales.

Conclusions

Inadequate model fit may indicate that these scales do not measure anxiety as a single dimension. Low/moderate correlation may indicate that these scales are incomparable and may conceptualize anxiety differently.

Keywords: anxiety during pregnancy; anxiety measurement scale; validity; measurement performance; confirmatory factor analysis; correlation

Background

Awareness of mental health issues surrounding childbirth has shifted from the narrow concept of 'postnatal depression' to a consideration of the spectrum of mental health issues that can occur during the perinatal period, one example of which is anxiety. Anxiety symptoms are common during pregnancy and impact up to 54% of women at some point during their pregnancies (54, 57, 78). The presence of clinically significant levels of anxiety during pregnancy can have adverse effects on maternal and birth outcomes, such as preterm birth, postpartum depression, and cognitive, behavioral, and emotional problems in offspring (54, 67, 80, 98).

Improved assessment and management of anxiety symptoms during pregnancy holds promise to improve women's mental health and birth outcomes. However, anxiety may be unrecognized in clinical practice. Assessment of anxiety symptoms may enhance recognition and thereby facilitate appropriate referral services or health interventions. Semi-structured diagnostic clinical interviews, considered reference standards for the diagnosis of anxiety disorders, are impractical to use for screening purposes in general clinical settings (59). Therefore, self-reported anxiety scales, considered screening tools, are commonly used to assess anxiety symptoms during pregnancy as they are simpler, shorter, and less expensive to implement, compared to clinical interviews (60, 63). However, most anxiety scales have been developed for general populations, and very few anxiety scales have been validated in pregnant populations against a reference standard for anxiety (60, 61, 63). This is important as many common signs and symptoms of pregnancy are similar to common signs and symptoms of anxiety (e.g. difficulty sleeping), potentially affecting the utility of anxiety screening tools in pregnant

women. Although some screening tools are considered better than others (60, 61, 63), no consensus exists regarding the most suitable anxiety screening scale for use in pregnancy (60, 61, 63), unlike depression where the EPDS addresses this gap.

In research, studies use a variety of self-reported scales for measuring anxiety during pregnancy (60, 62, 63); however, the information about the comparability of those scales in measuring anxiety is limited. The potentially incomparable findings across studies may dilute the evidence related to anxiety during pregnancy and limit the translation of evidence into policy recommendations and clinical and public health practices (130). The evaluation of multiple anxiety scales in the same sample of pregnant women can help to elucidate the suitability and comparability of anxiety scales in measuring anxiety during pregnancy.

Understanding the suitability and the comparability of anxiety scales has implications for anxiety screening in clinical and public health practices. For example, if scales have low agreement with each other when used in the same group of pregnant women, it suggests that future research should focus on reaching a consensus as to which anxiety scale(s) best reflect anxiety during pregnancy. We examined the performance of multiple anxiety scales (specifically, construct validity: factor and convergent validities) in measuring anxiety in pregnant women.

Methods

This study used data from two ongoing community-based prospective pregnancy cohort studies

being conducted in Alberta, Canada: All Our Families (AOF: n=3,341) and Alberta Pregnancy Outcomes and Nutrition (APrON: n=2,187). The description and comparability of these two cohort studies is described elsewhere (117, 118). Briefly, each cohort study had similar recruitment periods (2008-2012), inclusion criteria, sampling design, and data collection methods (117, 118). There were 231 women who had participated in both studies (overlapping sample). De-identified cohort datasets were obtained from SAGE (Secondary Analysis to Generate Evidence), a secure data repository developed by PolicyWise for Children & Families, which houses these datasets. Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary.

While both cohort studies measured anxiety during pregnancy using the EPDS-anxiety subscale (EPDS-3A), AOF also measured anxiety using the State-Trait Anxiety Inventory-State (STAI) 20-item scale, in which a subset of 6-items comprises a shortened scale, and APrON measured anxiety during pregnancy using anxiety subscale of the Symptoms Checklist-90 (SCL-90) (66, 68, 69, 75, 131). The EPDS-3A, the STAI-20, the STAI-6, and the SCL-90 are self-reported measures and they have their own factor structure, previously determined by factor analysis, measuring anxiety constructs (66, 68, 69, 75, 131). The EPDS-3A, comprising three items (3, 4, and 5) of the EPDS (90), has been suggested as a screening tool for anxiety (74, 75, 131), with a sensitivity of 66.70% and specificity of 88.20% in the postnatal population (75). The standard cut off score of 6 or more out of the EPDS-3A maximum score of 9 is used to classify women at risk of clinically significant levels of anxiety and who may benefit from referral to additional services (75). The STAI-20 scale is the full version of the STAI-S (includes 10 anxiety-present items and 10 anxiety-

absent items) (60, 67). It is the most commonly used measure of general anxiety in perinatal populations, with a reported sensitivity of 80.95% and specificity of 79.75% in the postnatal population (60, 67). The standard cut off score of 40 or more out of the STAI-20 maximum score of 80 is used to classify women at risk of clinically significant levels of anxiety (67). The STAI-6 scale is a short form of the STAI-S containing six items (items 1, 3, 6, 15, 16, and 17), which was identified in pregnant populations by Marteau and Bekker (68). The STAI-6 has been reported as a comparable scale of the full form of the STAI-S to measure anxiety in pregnant populations (68). The cut off for STAI-6 to classify women at risk of clinically significant levels of anxiety has not been identified. A 10-item anxiety subscale of the SCL-90 is considered a measure of general anxiety (69, 70, 132). Using the Derogatis criteria, the SCL-90 scale uses a mean score for each participant that is converted into normative T scores (71-73). Women with a T score of 63 or more are at risk for clinically significant levels of anxiety (72, 73). Both cohort studies measured anxiety in the second and third trimesters of pregnancy; however, for this analysis, we only examined anxiety data measured in second trimester of pregnancy as there were fewer missing data in this measurement.

Using previously determined factor structures of the four anxiety scales (the EPDS-3A, the STAI-20, the STAI-6, and the SCL-90) (66, 68, 69, 73, 131, 133), we tested the model goodness of fit for each scale (separately in each cohort sample). We used confirmatory factor analysis using structural equation modeling (SEM) for each anxiety scale, with maximum likelihood parameter estimation, to test the model goodness of fit for these scales (134-136). The SEM model included previously determined factor structure of each scale as the manifestations of latent

variable of anxiety (134, 135). The goodness of model fit was assessed using the indicators of fitness as suggested in the literature (134-136). The indicators of fitness include the comparative fit index (CFI>0.95, a cut off representing adequate model fit), the Tucker Lewis Fit index (TLI>0.95, a cut off representing adequate model fit), the root mean squared error of approximation (RMSEA<0.06, a cut off representing adequate model fit), and the standardized root mean squared residual (SRMR<0.08, a cut off representing adequate model fit) (134-136). Adequate model fit was considered if the model met the aforementioned cut-off representing adequate model fit (for the majority of fitness indicators), otherwise, inadequate model fit was considered.

We used the Spearman correlation coefficient and associated 95% confidence interval to estimate the correlation between the anxiety scores measured by multiple anxiety scales. We estimated Spearman correlations between the anxiety scores in the full sample (separately in each cohort sample). We also performed sensitivity analysis of Spearman correlations for anxiety scores using the sample who participated in both cohort studies (i.e., overlapping sample, n=231). This allowed us to examine the correlation between the anxiety scores measured by the four anxiety scales in the same sample, including the correlation of SCL-90 with STAI-20 and STAI-6 items scales. This was not possible using the full sample of the cohort studies as by design, women only completed the SCL-90 or the STAI-20/STAI-6, but not both. The correlation coefficients were interpreted based on the standard provided by Hinkle (137): negligible correlation for $r \leq 0.30$, low correlation for $0.30 < r \leq 0.50$, moderate correlation for $0.50 < r \leq 0.70$, high correlation for $0.70 < r < 0.90$, and very high correlation for $r \geq 0.90$. As the

four anxiety scales were built or have been used to measure the same construct (i.e., anxiety), a high to very high correlation (r >0.70) between the anxiety scores was expected.

Results

Women participating in the AOF and APrON cohorts were similar, with the majority of women being under the age of 35 years, married or living with a common-law partner, Caucasian, and approximately half of the women were primiparous (Table 4). The median STAI-20 anxiety score was 29, with an interquartile range (IQR) from 24 to 36, the median STAI-6 anxiety score was 9, with an IQR from 7 to 11, and the median SCL-90 anxiety score (raw score) was 0.2, with an IQR from 0.1 to 0.5. The median of EPDS-3A anxiety score was 2 (IQR from 1 to 4) and 3 (IQR from 1 to 4) in the AOF and APrON cohorts, respectively. The proportion of women classified as having clinically significant levels of anxiety by the EPDS-3A, the STAI-20, and the SCL-90 was 19.21% (95% CI=18.10, 20.32), 24.01% (95% CI=22.60, 25.61), and 12.13% (95% CI=10.61, 13.73), respectively. The proportion of women classified as having clinically significant levels of anxiety by the STAI-6 could not be assessed due to the lack of validated cut-off point. The inter-item correlations between items within the scales ranged from 0.42 to 0.58 (alpha=0.68) for the EPDS-3A, 0.13 to 0.63 (alpha=0.92) for the STAI-20, 0.38 to 0.65 (alpha=0.84) for the STAI-6, and 0.16 to 0.51 (alpha=0.82) for the SCL-90.

Table 4: Characteristics of Study Sample

	AOF cohort (n=3,341)[a]		APrON cohort (n=2,187)[a]		
	n (%)	95% CI	n (%)	95% CI)	p-value
Maternal age					0.028
<35yrs	2608 (80.52)	18.15, 20.88	1700 (77.91)	76.12, 79.60	
≥35yrs	631 (19.48)	79.11, 81.85	482 (22.09)	20.39, 23.88	
Marital status					0.008
Single/divorced/separated	185 (5.59)	4.86, 6.43	84 (4.00)	3.24, 4.92	
Married/common-law	3122 (94.41)	93.57, 95.14	2017 (96.00)	95.07, 96.76	
Ethnicity					0.190
White/Caucasian	2604 (78.74)	77.31, 80.10	1681 (80.24)	78.47, 81.88	
Others	703 (21.26)	19.90, 22.69	414 (19.76)	18.11, 21.52	
Duration of stay in Canada					0.066
<5 years	318 (9.65)	8.68, 10.70	165 (8.08)	6.97, 9.34	
Born in Canada/5 years+	2979 (90.35)	89.29, 91.32	1877 (91.92)	90.65, 93.02	
Body mass index					0.136
Underweight (<18.5 kg/m^2)	154 (4.73)	4.05, 5.51	67 (3.51)	2.77, 4.43	
Normal weight (18.5 - 24.99 kg/m^2)	1863 (61.37)	59.68, 63.20	1221 (63.99)	61.81, 66.12	
Overweight (25 - 29.99 kg/m^2)	661 (21.97)	20.58, 23.42	405 (21.23)	19.44, 23.12	
Obesity (≥30 kg/m^2)	359 (11.94)	10.86, 13.09	215 (11.27)	9.92, 12.77	
Parity					0.293
Primiparous	1686 (51.17)	49.46, 52.87	1184 (56.35)	54.22, 58.46	
Multiparous	1609 (48.83)	47.12, 50.54	917 (43.65)	41.53, 45.78	
Household income					0.877
<$40,000	295 (9.19)	8.24, 10.24	187 (9.00)	7.84, 10.30	
$40,000 - <$70,000	475(14.80)	13.61, 16.07	279 (13.43)	12.02, 14.96	
$70,000 - <$100,000	787 (24.52)	23.05, 26.04	466 (22.43)	20.68, 24.27	
≥$100,000	1653 (51.50)	49.76, 53.22	1016 (55.15)	53.00, 57.27	
Maternal education					0.006
High school or less than high school	363 (10.97)	9.94, 12.08	258 (12.39)	11.04, 13.88	
Some post-secondary	472 (14.26)	13.11, 15.50	405 (19.46)	17.81, 21.22	
Completed post-secondary	2474 (74.76)	73.25, 76.21	1418 (68.14)	66.10, 70.10	

AOF: All Our Familes; APrON: Alberta Pregnancy Outcomes and Nutrition

The standardized factor loadings of measurement variables or items for the EPDS-3A ranged from 0.58 to 0.79 in the AOF cohort and from 0.47 to 0.75 in the APrON cohort. For the STAI-20 scale, it ranged from 0.53 to 0.82 for the anxiety-absent items and 0.41 to 0.70 for the anxiety-present items. For the STAI-6 scale, it ranged from 0.76 to 0.86 for the anxiety-absent items and

0.63 to 0.73 for the anxiety-present items. For the SCL-90 scale, it ranged from 0.37 to 0.71. The factor loadings were all statistically significant ($p<0.0001$) for each anxiety scale (Appendix 5).

Table 5 shows goodness of model fit for each anxiety scale. Model fitness for the STAI-20 scale was inadequate as demonstrated by the root mean squared error of approximation (RMSEA=0.08), the comparative fit index (CFI=0.88), and the Tucker Lewis fit index (TLI=0.86), but was adequate based on the standardized root mean squared residual (SRMR= 0.06). Model fitness for the STAI-6 scale was adequate as demonstrated by the RMSEA=0.06, the CFI=0.99, the TLI=0.97, and the SRMR=0.02. Model fitness for the SCL-90 scale was inadequate (but was better than the STAI-20 scale) with RMSEA=0.07, CFI=0.92, TLI=0.90, and was adequate based on SRMR=0.04. Model fitness test for the EPDS-3A could not be assessed as it comprises only 3 items, which provided 0 degree of freedom and did not allow us to calculate the model fitness indicators.

Table 5: Model Goodness of Fit

Models	RMSEA	CFI	TLI	SRMR	Interpretation
Model that includes STAI-S scale's 20 items (AOF cohort)	0.08 (0.08, 0.08)	0.88	0.86	0.06	Inadequate
Model that includes STAI-S scale's 6 items (AOF cohort)	0.06 (0.05, 0.07)	0.99	0.97	0.02	Adequate
Model that includes SCL-90 anxiety scale's 10 items (APrON cohort)	0.07 (0.07, 0.08)	0.92	0.90	0.04	Inadequate

STAI-S: state trait anxiety inventory-state; SCL: symptom checklist; CFI: comparative fit index; TLI: Tucker Lewis fit index; RMSEA: Root mean squared error of approximation; SRMR: Standardized root mean squared residual; AOF: All Our Familes; APrON: Alberta Pregnancy Outcomes and Nutrition; Model fitness test for the Edinburgh postnatal depression scale anxiety subscale (EPDS-3A) was not applicable as it comprises only 3 items, which provided 0 degree of freedom and did not allow to calculate the model fitness indicators

As shown in Table 6, the correlation of EPDS-3A was moderate with both STAI-20 scale (r=0.57, 95% CI=0.54, 0.59) and STAI-6 scale (r=0.53, 95% CI=0.50, 0.55). The correlation between EPDS-3A and SCL-90 was low (r=0.44, 95% CI=0.41, 0.47). However, the correlation between STAI-20 and STAI-6 scales was very high (r=0.93, 95% CI=0.90, 0.95). A sensitivity analysis of the Spearman correlation in the sample who participated in both cohort studies showed similar results (Table 3). Additionally, the sensitivity analysis revealed low correlation of SCL-90 with both STAI-20 (r=0.37) and STAI-6 scales (r=0.36).

Table 6: Relationship between the Anxiety Scores Measured by Four Anxiety Scales

	AOF (n=3,341) or APrON (n=2,187) full cohort		Overlapped cohort[d] (n=231)	
Description	**r[a] (95% CI)**	**Interpretation**	**r[a] (95% CI)**	**Interpretation**
Anxiety scores measured by STAI-S 20-item and EPDS-3A scales	0.57[b] (0.54, 0.59)	Moderate correlation	0.52 (0.41, 0.62)	Moderate correlation
Anxiety scores measured by STAI-S 6-item and EPDS-3A scales	0.53[b] (0.50, 0.55)	Moderate correlation	0.46 (0.34, 0.56)	Low correlation
Anxiety scores measured by SCL-90 and EPDS-3A scales	0.44[c] (0.41, 0.47)	Low correlation	0.35 (0.22, 0.47)	Low correlation
Anxiety scores measured by STAI-S 6-item and STAI-S 20-item scales	0.93[b] (0.93, 0.95)	Very high correlation	0.90 (0.87, 0.92)	Very high correlation
Anxiety scores measured by STAI-S 20-item and SCL-90 scales	Unfeasible	-	0.37 (0.25, 0.49)	Low correlation
Anxiety scores measured by STAI-S 6-item and SCL-90 scales	Unfeasible	-	0.36 (0.24, 0.48)	Low correlation

[a]Spearman correlation coefficient; CI: confidence interval; [b]AOF: All Our Familes; [c]APrON: Alberta Pregnancy Outcomes and Nutrition; [d]sample who participated in both cohort studies; EPDS-3A: Edinburgh postnatal depression scale anxiety scale; STAI-S: state trait anxiety inventory-state; SCL: symptom checklist

Discussion

This study evaluated the performance of multiple anxiety screening scales in pregnant women in Alberta, Canada. The STAI-6 scale had adequate model fit, whereas, the STAI-20 scale and the SCL-90 scale had inadequate model fit as demonstrated by the majority of indicators of fitness. The correlation between the EPDS-3A and the STAI-20 scale, the STAI-6 scale, and the SCL-90 scale were low to moderate. The correlation of SCL-90 scale with the STAI-20 scale and the STAI-6 scale was low. The correlation between STAI-20 and STAI-6 scales was very high.

This study clarifies the construct validity (factor and convergent validity) of existing anxiety screening scales that are being used in pregnant women. The goodness of fit findings suggest

that the STAI-6 scale may provide the most utility in assessing anxiety among pregnant women. The findings also indicate that the scales may be measuring different aspects of anxiety during pregnancy. This mirrors that these scales may conceptualize the anxiety construct differently and/or may measure constructs that are different from anxiety (62, 64). The scales' differences in anxiety conceptualization may arise due to multiple issues related to measuring different aspects or dimensions of anxiety, different content or adequacy of anxiety measurement items, and appropriateness of items during pregnancy. To illustrate, the SCL-90 scale and the STAI-20 scale were originally developed for, and validated in, general populations. The SCL-90 scale assesses general symptoms of anxiety psychopathology over past 7 days (69), whereas, the STAI-20 scale assesses individual's feelings of anxiety at this moment (66). The STAI-20 scale also includes somatic symptoms related items (for example, I feel comfortable and I feel at ease) that are also commonly affected as a consequence of pregnancy. The STAI-6 scale, a short version of STAI-20 scale, excludes these somatic items and consequently may be better able to distinguish anxiety from physiologic changes due to pregnancy. The EPDS-3A, which comprises 3 items of the screening tool, EPDS, was identified based on its sensitivity to perinatal anxiety, and may not distinguish anxiety from depression (74, 75, 131). As shown by a previous validation study, the EPDS-3A is an insensitive anxiety scale (sensitivity=66.7%) (75), yet the scale reveals a high prevalence of anxiety in our study – suggesting its poor specificity.

Our findings may explain the wide variation in prevalence estimates of anxiety during pregnancy and the inconsistencies in its association with adverse pregnancy outcomes and child development in the literature (54, 57, 78-82). While the discrepancies in research findings may

occur due to differences in sample characteristics across studies or over time, it may also relate in part to the scales used (62). Our findings, based on the evaluation of multiple anxiety scales in the same sample, support that some of the variation may be attributable to use of different anxiety scales. Our findings are unlikely due to the different population characteristics; thus, it highlights the opportunity for a consensus as to which tools are best used to screen for and subsequently diagnose anxiety during pregnancy. As anxiety experienced during pregnancy may differ from generalized anxiety (60, 63), a thorough examination of existing anxiety scales vis a vis pregnancy, including content and criterion validities in addition to the construct validity, should be a first approach. While we desire a simple, rapid, inexpensive, and safe anxiety screening scale in a clinical/research setting, it must be balanced with a high degree of criterion validity.

Our finding regarding the low correlation between the EPDS-3A and other anxiety scales is supported by a previous study that was conducted in pregnant women (73). We could not find studies that assessed fitness (confirmatory factor analysis) of the anxiety scales in pregnant women (60, 61, 63), except the STAI-6 scale (68). The STAI-6 scale best suited our data and showed a high correlation with the STAI-20 scale. Some items of the STAI-20 scale did not contribute enough to the scale (low factor loadings), whereas, items of the STAI-6 scale were highly sensitive to the anxiety construct (high factor loadings) (66). These results are consistent with a previous study done in pregnant women (68) and the Spielberger's findings on STAI-20 scale (66). The use of a short scale maximizes response rates, and minimizes the number of response errors and unanswered items; thus, it improves the validity and generalizability of

findings. It also overcomes barriers in assessing anxiety in clinical practices, such as lack of time and resources. Of note, the STAI-20 scale has been validated in pregnant populations against a clinical interview, and has shown a good criterion validity (67). However, the validity of the STAI-6 scale against a clinical interview has not yet been evaluated, the scale lacks a cut off score to indicate a clinically significant anxiety, which is essential before its routine adoption (as a screening tool) into clinical practice.

This study used a pragmatic approach by analyzing anxiety data from two comparable large community-based pregnancy cohort studies (analysis in two full cohorts and in the overlapped cohort). This permitted us to evaluate and compare four anxiety scales in a comparable sample of pregnant women, which, to our understanding, has not been done. The findings are relevant given the value of identifying women with anxiety during pregnancy who may benefit from specific supports or interventions. However, this study could not assess clinical utility or relative superiority of these scales in detecting clinically significant levels of anxiety in the same/comparable sample of pregnant women due to the lack of a reference standard for criterion validation (e.g., structured clinical diagnostic interview). The future assessment of criterion validity is needed for this propose. The criterion validity assessment estimates a scale's sensitivity, specificity, and predictive values to identify its clinical utility, and takes into account the somatic aspects of pregnancy to further confirm the scale's value for use in pregnancy. This study examined the suitability of a priori identified factor structures of the most commonly used anxiety scales in pregnant populations (using confirmatory factor analysis), but it did not explore other possible factor structure(s) or dimension(s) that may be suitable in pregnancy.

Our sample involves an over-representation of women with high socioeconomic status, while this homogenous sample provided an ideal condition to compare the scales, it may limit the generalizability of the findings to other demographic groups. However, our sample is representative of the pregnant and parenting population in urban Canada (57, 118).

Conclusions

The STAI-6 scale had adequate suitability, and the STAI-20 scale and the SCL-90 scale had inadequate suitability in measuring anxiety in pregnant women. The suitability of the EPDS-3A could not be tested. These scales were non-equivalent to each other (except the equivalency between the STAI-20 and STAI-6 scales) in measuring anxiety in pregnant women. This indicates that these scales are different: they may not measure anxiety as a single dimension and/or may conceptualize anxiety differently in pregnant women. Overall, identification and management of anxiety during pregnancy is a key to promote maternal mental health and consequently health outcomes of their infants. Availability of an anxiety scale (with adequate content, construct, and criterion validities) that is nuanced to the condition of pregnancy may enable optimal identification of women who would benefit from supports and services. An attention towards the usefulness of pregnancy-specific anxiety scales, which conceptualize anxiety during pregnancy as a different construct from the construct of general anxiety, may be needed.

Chapter 5: Neighbourhood Socioeconomic Status Modifies the Association between Anxiety and Depression during Pregnancy and Preterm Birth: A Community-based Canadian Cohort Study

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Abstract

Background

The association between anxiety and depression during pregnancy and preterm birth (PTB) is incompletely understood. This study examined the association of anxiety alone, depression alone, and the presence of both anxiety and depression with PTB and further examined whether neighbourhood socioeconomic status (SES) modified this association.

Methods

Individual data from two pregnancy cohort studies in Alberta, Canada (n=5,538) were linked to neighbourhood SES data from Canada census. Depression was defined as an Edinburgh Postnatal Depression Scale (EPDS) score of ≥13, anxiety was defined as an EPDS-anxiety subscale score of ≥6, and the presence of both anxiety and depression was defined as meeting both anxiety and depression definitions. Logistic regression models were developed including confounding variables (parity, ethnicity, and body mass index) and the interaction between neighbourhood deprivation and anxiety/depression.

Results

Overall, 7.26% of women delivered preterm infants. The presence of both anxiety and depression, but neither of these conditions alone, was significantly associated with PTB (OR=1.57, 95% CI=1.07, 2.29) and had significant interaction with neighbourhood deprivation (p-value=0.014). Compared to women without anxiety and depression, women with both anxiety and depression who lived in quintile 3 and more deprived neighbourhoods had

significantly increased odds of experiencing a preterm delivery (quintile 4 and 5: OR=2.19, 95% CI=1.33, 4.12). Whereas, compared to women without anxiety and depression, women with both anxiety and depression who lived in the least deprived neighbourhood were not at elevated odds of experiencing a preterm delivery (OR=0.17, 95 % CI=0.02, 1.28). The predicted probability of PTB for women with both anxiety and depression was 10.00%, which increased to 15.71% if they lived in the most deprived neighbourhoods and decreased to 1.41% if they lived in the least deprived neighbourhoods.

Conclusions

Effects of anxiety and depression on the risk of PTB differ depending on where women live. This understanding may guide the identification of women at increased risk for PTB and allocation of resources for early identification and management of anxiety and depression.

Keywords: anxiety, depression, neighbourhood socioeconomic status, deprivation, preterm birth

Background

Worldwide, a total of 15 million births occur preterm (i.e., before 37 weeks of gestation), with a global average rate of 11.1% (6). Preterm birth (PTB) is responsible for 35% of neonatal deaths globally (1). Among survivors, it is also a significant risk factor for short and long-term morbidities, such as respiratory distress syndrome, cerebral palsy, and learning difficulties (2-4). Despite substantial research and interventions to prevent PTB, the incidence of PTB has not declined and its etiology remains unclear (5, 6). Understanding the risk factors for PTB, such as psychosocial distress and low neighbourhood level socioeconomic status (SES), may help identify women at increased risk, and assist in the allocation of resources, ultimately reducing the incidence of PTB.

PTB has been linked to psychosocial distress during pregnancy, specifically anxiety and depression – the most common mental health problems during pregnancy (80, 82, 95, 102). However, the association between anxiety and depression during pregnancy and PTB is incompletely understood. Many previous studies on the association between anxiety and depression and PTB were conducted in medical settings (i.e. hospital and clinic) with small samples and high rates of attrition (80, 82, 102). Notably, most of the previous studies analyzed anxiety or depression in isolation without considering that they may occur in a comorbid state (79, 80, 82, 95, 102). Comorbid anxiety and depression is, in fact, common (affecting up to 50% of women with anxiety or depression) and is more likely to involve severe symptoms of anxiety and depression than isolated anxiety or depression (103, 107, 138). Thus, comorbid anxiety and

depression may pose a higher risk of PTB than isolated anxiety or depression, which may influence the association between anxiety or depression and PTB.

Anxiety and depression are negatively correlated with neighbourhood SES (111). Neighbourhood SES is an area level measure of SES, which aggregates individual SES (such as income, education, and employment status) at a certain geographical level (24). Neighbourhood SES may influence the risk of PTB by exposing women to health benefitting or risk elevating factors (22, 24, 27, 28). Low neighbourhood SES may affect an individual's ability to fulfill daily needs, access resources, make lifestyle choices, and cope with different situations (22, 24, 27, 28). Thus, the risk of PTB that is associated with anxiety and/or depression during pregnancy may differ by neighbourhood SES. To our knowledge, this has not been examined.

This study examined the association of the presence of anxiety symptoms alone, depression symptoms alone, and both anxiety and depression symptoms with PTB. This study further examined whether the presence of anxiety, depression, and both anxiety and depression interact with neighbourhood SES to increase the risk of PTB. This may help to determine the subgroups of women who are at increased risk for PTB.

Methods

Data sources

This study combined datasets from two community-based prospective pregnancy cohort studies in Alberta, Canada (n=5,528). The All Our Families (AOF) cohort study recruited 3,341

pregnant women and the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort study recruited 2,187 pregnant women, with 231 women participating in both studies. Both studies collected data on socio-demographics, lifestyle, social support, anxiety, depression, and PTB. (117) The description and comparability of these two cohort studies is available elsewhere (117, 118), and justifies combining these data sources (114). Briefly, each cohort study had similar recruitment periods (2008-2012), inclusion criteria, sampling design, and data collection methods (117, 118). We obtained two de-identified cohort datasets linked with neighbourhood SES data from SAGE (Secondary Analysis to Generate Evidence), the secure data repository developed by PolicyWise for Children & Families, which houses these datasets. Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary.

Variables that were deemed similar in the two studies were harmonized and appended into a single new dataset. Women who participated in both studies (n=231) were counted only once. Both cohorts used an identical measure of depression, i.e., the Edinburgh Postnatal Depression Scale (EPDS). The EPDS is a 10-item self-reported scale with each item ranging from 0 to 3 to assess symptoms of current depression (i.e. how women have felt in the past 7 days) (90). The EPDS has high internal consistency of 0.87 (90), a sensitivity of 78%, and specificity of 99% in the obstetric population (91, 92), and is the most common scale used to measure antenatal and postnatal depression (89). The recommended standard cut-off score of ≥13 out of 30 points on the EPDS was used to define the presence of clinically significant depression during pregnancy (93). While the EPDS was specifically designed to assess depression, three items (namely items

3, 4, and 5) comprising the anxiety subscale (EDPS-3A) have been suggested as a measure of anxiety (74, 75), with a sensitivity of 66.70% and specificity of 88.20% in the obstetric population (75). The standard cut-off of ≥6 out of a maximum of 9 is used to define the presence of clinically significant anxiety during pregnancy (75). The cohort studies used different measures of anxiety: the AOF study used the State-Trait Anxiety Inventory and the APrON study used the Symptoms Checklist-90. Thus, the EPDS-3A was chosen as a measure of anxiety to have a consistent measure across studies and to avoid the introduction of misclassification bias related to the use of different tools. Presence of both anxiety and depression was defined as meeting both anxiety and depression definitions at the same time point in pregnancy. The birth that occurred before the 37 weeks of gestation was defined as PTB (both spontaneous and iatrogenic included).

Neighbourhood SES data were measured by the Pampalon material deprivation index (derived from the 2011 Statistics Canada census) (25, 121), which were aggregated at the dissemination area (DA) level. DA is the smallest geographical unit available in the Canadian census, consisting of 400-700 persons (26). The Pampalon material deprivation index is a composite measure of neighbourhood SES that combines the proportion of persons without high school diplomas, the average personal income, and the rate of unemployment within the DA. It is used as a quintile, with quintile 1 representing the least deprived and quintile 5 representing the most deprived neighbourhoods (25).

Data Analysis

First, variables significantly associated with PTB as well as anxiety and depression were identified using bivariate analysis ($p<0.05$). Then, a multivariable logistic regression model for the association between anxiety and/or depression ("anxiety only," "depression only," and "both anxiety and depression") and PTB was constructed. The model included variables identified in the bivariate analysis (parity, ethnicity, and body mass index), other variables (smoking, social support, and maternal SES: these variables were selected based on literature, considering that they may influence the association in the multivariable model), and interaction terms. The interaction terms comprised "anxiety only," "depression only," and "both anxiety and depression" combined with each quintile of deprivation indices. Quintile 4 and 5 were combined as there were few or no cases in some strata. The presence of significant interactions was identified through the p-values associated with beta coefficients of each interaction term.

Variables were dropped from the model using a stepwise backward variable elimination approach if they did not influence the association between anxiety and/or depression and PTB. The interaction terms and variables (parity, ethnicity, and body mass index) were retained in the model as some of the interaction terms were significant and the variables influenced the association. This approach (limiting the variables in the model) adjusted for confounding and improved the precision of the estimates. Subsequently, we constructed another model without the interaction terms. A likelihood ratio test was used to compare the goodness of model fit between those two nested models – with and without the interaction terms. Adjusted prediction of PTB (i.e., predicted probability of PTB that was evaluated at the average value of

covariates, parity, ethnicity, and body mass index, across observations) was estimated using the model with interaction terms. Missing data were deleted using variable-wise or pair-wise deletion approach for univariate or bivariate analysis and listwise deletion approach for regression models. Alpha (α) of <0.05 was used to determine statistical significance. All analyses were performed using STATA/IC 14.1.

Results

Of total 5,297 pregnant women, the proportion of missing data ranged from 1.52% for depression to 7.51% for gestational age at delivery. Overall, 7.26% (95% CI=6.57, 8.07) of women delivered preterm infants. Women who delivered preterm infants were more likely to be non-white, obese, primiparous, and from the most deprived neighbourhoods. As shown in Table 7, 17.9% of women had anxiety and/or depression: 7.70% (95% CI=7.01, 8.42) of women had both anxiety and depression, followed by 6.01% (95% CI=5.14, 6.62) of women who had anxiety alone, and 4.19% (95% CI=3.70, 4.81) of women who had depression alone. Women with both anxiety and depression had a higher rate of PTB (10.60%, 95% CI=7.78, 14.29) compared to those with isolated anxiety (6.51%, 95% CI=4.19, 9.97) or isolated depression (8.16%, 95% CI=5.06, 12.91) or without anxiety and depression (6.89%, 95% CI=6.14, 7.72). A higher proportion of women with both anxiety and depression (compared to those with anxiety or depression alone) were single, non-white, recent immigrants, had a low household income, and were from the most deprived neighbourhoods ($p<0.05$) (Table 1). Mean scores for anxiety (6.60±0.41) and depression (16.21±0.13) were higher among women with both conditions compared to those with anxiety alone (6.12±0.20) or depression alone (14.61±0.12).

Table 7: Distribution of Maternal Characteristics across Anxiety and Depression Status during Pregnancy

Maternal characteristics	**Absence of both anxiety and depression n=4294 (82.10%)**	**Presence of anxiety only n=312 (6.01%)**	**Presence of depression only n=220 (4.19%)**	**Presence of both anxiety and depression n=402 (7.70%)**	$\chi 2$ **p-value**
	n (%, 95% CI)	**n (%, 95% CI)**	**n (%, 95% CI)**	**n (%, 95% CI)**	
Maternal age ≥35yrs	886 (21.00, 19.79-22.26)	48 (15.53, 11.91-22.01)	59 (27.44, 21.89-33.79)	71 (18.39, 14.84-22.58)	0.006
Marital status					
Single/divorced/separated	168 (3.95, 3.41-4.58)	22 (7.19, 4.78-10.68)	25 (11.47, 7.87-16.42)	47 (11.81, 8.99-15.37)	<0.0001
Ethnicity					<0.0001
Non-white	807 (19.02, 17.86-20.22)	68 (22.15, 17.85-27.14)	67 (30, 88, 25.08-37.33)	143 (36.11, 31.52-40.96)	
Duration of stay in Canada					<0.0001
Born/5 years+	3841 (91.61, 90.73-92.41)	275 (89.87, 85.95-92.78)	185 (87.26, 82.06-91.12)	329 (84.36, 80.41-87.64)	
<5 years	352 (8.39, 7.59-9.27)	31 (10.13, 7.21-14.05)	27 (12.74, 8.87-17.94)	61 (15.64, 12.36-19.59)	
Body mass index					0.002
Underweight (<18.5kg/m^2)	170 (4.21, 3.63-4.88)	12 (4.08, 2.33-7.05)	11 (5.26, 2.94-9.25)	21 (5.57, 3.66-8.39)	
Normal weight (18.5 - 24.99 kg/m^2)	2552 (63.23, 61.73-64.70)	172 (58.50, 52.78-64.00)	125 (59.81, 53.02-66.24)	220 (58.36, 53.30-63.23)	
Overweight (25 - 29.99 kg/m^2)	882 (21.85, 20.60-23.15)	59 (20.07, 15.87-25.04)	50 (23.92, 18.62-30.17)	73 (19.36, 15.68-23.66)	
Obesity (≥30 kg/m^2)	432 (10.70, 9.79-11.69)	51 (17.35, 13.43-22.11)	23 (11.00, 7.42-16.01)	63 (16.71,13.27-20.82)	
Parity					<0.0001
Primiparous	2106 (49.66, 48.15-51.16)	109 (35.39, 30.24-40.89)	111 (51.15, 44.51-57.74)	190 (48.10, 43.21-53.03)	
Unintended pregnancy	742 (17.44, 16.33-18.61)	70 (22.65, 18.33-27.65)	72 (32.88, 26.98-39.37)	122 (30.65, 26.32-35.36)	<0.0001
Smoked before pregnancy	822 (19.33, 18.17-20.55)	86 (27.92, 23.19-33.20)	61 (27.98, 22.42-34.31)	123 (30.90, 26.56-35.62)	<0.0001
Alcohol consumption before pregnancy	3603 (84.72, 83.60-85.77)	268 (87.01, 82.77-90.33)	181 (82.65, 77.05-87.11)	305 (76.63, 72.22-80.53)	<0.0001
Drug abuse before pregnancy	561 (13.19, 12.21-14.24)	61 (19.87, 15.78-24.71)	44 (20.37, 15.52-26.27)	83 (20.85, 17.14-25.13)	<0.0001
Maternal education					<0.0001
≤High school	451 (10.63, 9.74-11.60)	49 (16.23, 12.48, 20.82)	42 (19.44, 14.70, 25.27)	68 (17.30, 13.87, 21.37)	
Some post-secondary	669 (15.77, 14.70-16.90)	57 (18.87, 14.85-23.69)	35 (16.20, 11.87-21.73)	96 (24.43, 20.43-28.92)	
Completed post-secondary	3121 (73.59, 72.24-74.90)	196 (64.90, 59.35-70.07)	139 (64.35, 57.74-70.46)	229 (58.27,53.33-63.05)	

Maternal characteristics	**Absence of both anxiety and depression n=4294 (82.10%)**	**Presence of anxiety only n=312 (6.01%)**	**Presence of depression only n=220 (4.19%)**	**Presence of both anxiety and depression n=402 (7.70%)**	$\chi 2$ **p-value**
	n (%, 95% CI)	**n (%, 95% CI)**	**n (%, 95% CI)**	**n (%, 95% CI)**	
Household income					<0.0001
<$40,000	325 (7.82, 7.04-8.67)	25 (8.39, 5.73-12.12)	40 (18.60, 13.95-24.37)	85 (22.02, 18.16-26.43)	
$40,000 - <$70,000	542 (13.04, 12.84-14.10)	53 (17.79, 13.84-22.55)	43 (20.00, 15.18-25.88)	83 (21.50, 17.68-25.88)	
$70,000 - <$100,000	989 (23.79, 22.52-25.11)	76 (25.50, 20.87-30.76)	52 (24.19, 18.93-30.36)	85 (22.02, 18.16-26.43)	
≥$100,000	2301 (55.35, 53.84-56.86)	144 (48.32, 42.69-53.99)	80 (37.21, 31.00-43.86)	133 (34.46, 29.88-39.34)	
Inadequate social support anytime during pregnancy	731 (17.13, 16.03-18.29)	77 (25.00, 20.48-30.14)	127 (57.37, 51.34-64.35)	210 (52.37, 47.47-57.22)	<0.0001
Neighbourhood deprivation index					<0.0001
Quintile 1 (least deprived)	1108 (27.70, 26.33-29.10)	68 (24.29, 19.61-29.65)	51 (24.88, 19.43-31.25)	80 (22.35, 18.32-26.95)	
Quintile 2	1045 (26.13, 24.78-27.51)	82 (29.29, 24.25-34.88)	41 (20.00, 15.08-26.04)	83 (23.18, 19.10-27.84)	
Quintile 3	800 (20.00, 18.79-21.27)	64 (22.86, 18.31-28.14)	39 (19.02, 14.22-24.98)	65 (18.16, 14.50-22.50)	
Quintile 4	618 (15.45, 14.36-16.60)	37 (13.21, 9.72-17.71)	30 (14.63, 10.42-20.16)	47 (13.13,10.00-17.04)	
Quintile 5 (most deprived)	429 (10.72, 9.80-11.72)	29 (10.36, 7.29-14.50)	44 (21.46, 16.37-27.61)	83 (23.18,19.10-27.84)	
Preterm birth	276 (6.89, 6.14-7.72)	19 (6.51, 4.19-9.97)	16 (8.16, 5.06-12.91)	37 (10.60, 7.78-14.29)	0.068

Sample size between variables differs as missing values were deleted using variable wise or pair wise deletion approach

The presence of both anxiety and depression (adjusted odds ratio (aOR)=1.57, 95% CI=1.07, 2.29), but neither anxiety alone (aOR=0.85, 95% CI=0.51, 1.41) nor depression alone (aOR=1.28, 95% CI=0.75, 2.18), was significantly associated with PTB (Table 2). Effect modification was observed between the presence of both anxiety and depression and neighbourhood SES (specifically, neighbourhood with deprivation quintile 4 and 5 combined, p-value=0.014, and deprivation quantile 3, p-value=0.015). Compared to women without anxiety and depression, women with both anxiety and depression who lived in quintile 3 and more deprived neighbourhoods had significantly increased odds of experiencing a preterm delivery (quintile 4 and 5: aOR=2.19, 95% CI=1.33, 4.12). Whereas, compared to women without anxiety and depression, women with both anxiety and depression who lived in the least deprived neighbourhood were not at elevated odds of experiencing a preterm delivery (aOR=0.17, 95 % CI=0.02, 1.28) (Table 8).

Table 8: Association between Anxiety and Depression Status during Pregnancy and Preterm Birth[a]

Anxiety and depression status during pregnancy[b]	**Overall OR (95%CI)**	**Stratified by neighbourhood deprivation indices (quintile)**			
		Quintile 1[c] OR(95%CI)	**Quintile 2 OR (95%CI)**	**Quintile 3 OR (95%CI)**	**Quintile 4 and 5[d] OR (95%CI)**
Presence of anxiety only	0.85 (0.51, 1.41)	0.65 (0.24, 1.98)	0.72 (0.25, 2.05)	1.05 (0.36, 2.99)	1.03 (0.41, 2.78)
Presence of depression only	1.28 (0.75, 2.18)	0.62 (0.18, 1.95)	0.89 (0.20, 3.85)	1.88 (0.76, 6.60)	2.67 (0.99, 7.37)
Presence of both anxiety and depression	1.57 (1.07, 2.29)	0.17 (0.02, 1.28)	1.38 (0.57, 3.36)	2.68 (1.25, 6.14)	2.29 (1.33, 4.12)

[a]Adjusted for parity, ethnicity, and body mass index; [b]absence of both anxiety and depression as a reference group; [c]quintile 1: least deprived neighbourhood; [d]quintile 5: most deprived neighbourhood (quintile 4 and 5 were combined due to few or no cases in some strata); OR: odds ratio; CI: confidence interval

As shown in Table 9, the predicted probability of PTB for women with a presence of both anxiety and depression was 10.00% (95% CI=6.77, 13.09). It increased to 15.71% (95% CI=9.45, 22.63) if they lived in the most deprived neighbourhoods – an increase of 57.10% – and it decreased to 1.41% (95% CI=0.04, 4.16) if they lived in the least deprived neighbourhoods. The predicted probability of PTB for women with depression alone was 9.64% (95% CI=5.15, 14.12), which increased to 14.03% (95% CI=2.74, 25.33) if they lived in the most deprived neighbourhoods. The predicted probability for women with anxiety alone and women with absence of anxiety and depression remained similar across the neighbourhood deprivation indices.

Table 9: Predicted Marginal Prevalence of Preterm Birth[a]

Anxiety and depression status during pregnancy[b]	**Overall % (95%CI)**	**Stratified by neighbourhood deprivation indices (quintile)**			
		Quintile 1[b] % (95%CI)	**Quintile 2 % (95%CI)**	**Quintile 3 % (95%CI)**	**Quintile 4 and 5[c] % (95%CI)**
Absence of both anxiety and depression	7.12 (6.77, 13.09)	7.57 (5.58, 9.25)	6.37 (4.76, 7.91)	6.95 (5.06, 8.84)	7.56 (5.87, 9.26)
Presence of anxiety only	6.25 (3.31, 9.07)	5.45 (0.24, 10.67)	4.87 (0.27, 9.53)	6.54 (0.34, 12.74)	7.91 (1.25, 14.57)
Presence of depression only	9.64 (5.15, 14.12)	4.74 (0.50, 10.41)	5.69 (0.45, 13.42)	13.31(3.43,23.18)	14.03 (2.74, 25.33)
Presence of both anxiety and depression	10.00 (6.77, 13.09)	1.41 (0.04, 4.16)	8.01 (1.87, 14.14)	15.97 (6.32,25.63)	15.71 (9.45, 22.63)

[a]Adjusted for parity, ethnicity, and body mass index; [b]quintile 1: least deprived neighbourhood; [c]quintile 5: most deprived neighbourhood (quintile 4 and 5 were combined due to few or no cases in some strata); OR: odds ratio; CI: confidence interval

Discussion

Main Findings

This study examined the association of anxiety alone, depression alone, and the presence of both anxiety and depression during pregnancy with PTB, using data from two community-based pregnancy cohort studies in Alberta, Canada. The study found an association between the presence of both anxiety and depression and PTB, which significantly differed according to neighbourhood SES. Women with both anxiety and depression were more likely to deliver preterm infants if they lived in a relatively more deprived neighbourhood compared to if they lived in a less deprived neighbourhood. For women with both anxiety and depression, the absolute predicted probability of delivering preterm infants was 16% if these women lived in the most deprived neighbourhood and it was 1% if they lived in the least deprived neighbourhood. Overall, the findings suggest the importance of neighbourhoods on maternal health (in general) and more specifically PTB.

Interpretation

Although few previous studies assessed the association between the presence of both anxiety and depression during pregnancy and PTB, our findings are consistent in that the presence of both anxiety and depression increases the risk of PTB (103, 108, 139). This may be related to the additive effects of prenatal depression and anxiety and the effects of severity of anxiety and depressive symptoms. Similar to our study, previous studies conducted in the general population and in pregnant women found a higher score of anxiety or depression symptoms among those with both anxiety and depression than those with isolated anxiety or depression

(108, 140). It is also reported in previous studies that individuals with both anxiety and depression have longer depressive episodes, worse psychosocial impairment, poorer response to medication, compromised quality of life, and increased suicidality than those with isolated anxiety or depression (138-140). Thus, the presence of both anxiety and depression during pregnancy may lead to an increased risk of poor birth outcomes, including PTB, than depression or anxiety alone.

Our study did not find an association between anxiety alone or depression alone and PTB, which is consistent with previous studies that analyzed isolated anxiety or depression separately from the presence of both or comorbid anxiety and depression (103, 108). However, the finding is inconsistent with several previous studies that analyzed anxiety or depression intermixing with the presence of both conditions (82, 95). It is possible that the association described in the literature requires high levels of anxiety or depression, which is more likely present in the presence of both anxiety and depression symptoms or disorders. Thus, the associations found in previous studies may have been confounded by the presence of both anxiety and depression symptoms or comorbid anxiety and depression disorders. The increased risk of PTB associated with the presence of both anxiety and depression (but not with isolated anxiety or depression) may, in part, explain the inconsistencies across previous findings on the association between prenatal anxiety or depression and PTB. Similarly, previous studies did not analyze the association stratified by neighbourhood SES, meaning that these studies averaged the association across neighbourhood SES, which may also explain the inconsistencies across previous studies findings.

A strong association between the presence of both anxiety and depression and PTB among women living in a relatively more deprived neighbourhood may reflect that, besides individual level risk factors, the risk of PTB is related to neighbourhood factors (22, 24, 27). For example, women living in deprived neighbourhoods often have less access to healthy foods, quality health services, and opportunities for leisure activity, and have more exposure to societal stressors and crimes (22, 24, 27, 28). Anxious and depressed women living in less advantaged areas may interpret the deprivation associated stressors more acutely and have less support or are less able to manage or cope with their stressors, making them severely emotionally distressed compared to those living in more advantaged areas (79, 95, 112, 113). Consequently, the elevated risk of delivering preterm is more likely to occur in this group of women. However, it is important to note that, the relationship between mental illness and impoverishment is difficult to interpret as causal, given the bi-directional relationship between them. Furthermore, in our study, the group of women with both anxiety and depression (who often have severe symptoms of anxiety or depression) in the least deprived neighbourhoods had an exceptionally low rate of PTB. The observed association between the presence of both anxiety and depression and PTB among women living in a relatively more deprived neighbourhood seems to depend on this result. Thus, the replication of this finding seems important.

Strengths and Limitations

To our knowledge, few studies have directly examined the presence of both depressive and anxious symptoms versus isolated depressive or anxious symptoms as risk factors of PTB, and no studies have examined neighbourhood SES as a modifier to the relationship between anxiety

and/or depression and PTB. This study is important given its focus on the commonest psychological condition (i.e., comorbid anxiety and depression) and the importance of identification of specific groups of women who may benefit the most from the preventive interventions. This study used two community-based prospective pregnancy cohort studies. This provided an opportunity to describe PTB across the several strata of anxiety, depression, and both anxiety and depression and neighbourhood SES in a relatively representative sample (compared, for example, to a hospital- or clinic-based sample) of pregnant women. However, even using the two cohorts, some strata had few cases of preterm births, which may have led to the observed imprecise and/or insignificant estimates (specifically in a group with depression alone). As these cohorts over-represent women with high SES (57, 118, 129), it limits the generalizability of the findings to other demographic groups. While the use of prospective measurement of depression and anxiety reduces the chance of misclassifications due to recall bias, the use of self-reported anxiety and depression measurement scales (specifically, the EPDS-3A scale) may have introduced measurement inaccuracy. Furthermore, the EPDS-3A is a subscale of the EPDS. The standard cut-off point for the EPDS excluding the items of the EPDS-3A has not been established. While the use of a single scale may overestimate the presence of anxiety and/or depression, being able to identify combined anxiety and depression group using a single scale is advantageous as it facilitates for intervention design. While we examined the association between anxiety and/or depression and PTB analyzing the influence of several potential confounders, other confounders such as antidepressant use, other psychiatric conditions, and medical risk factors that may influence the associations were not considered due to data limitation. Similarly, we were not able to separate out spontaneous and iatrogenic

PTB in the model – the association might be stronger with a focus on spontaneous PTB. Overall, replication of this study addressing these limitations may further the understanding on risk factors and preventive strategies of PTB.

Conclusions

Our study found that the presence of both prenatal anxiety and depression increases the risk of PTB and the risk is higher for women living in low SES neighbourhoods compared to women living in high SES neighbourhoods. The finding informs that an intervention strategy that focuses on a group of women with a presence of both anxiety and depression and living in the most deprived neighbourhood may reduce the risk of PTB. Furthermore, future research that examines the influence of severity of anxiety and depression on risk of PTB may further the understanding on risk factors and preventive strategies of PTB. A strategy that identifies and manages anxiety and depression prior to pregnancy should be a priority

Chapter 6: Synthesis and Overriding Conclusions

This research examined modifiable risk factors for preterm birth (PTB), particularly, neighbourhood socioeconomic status (SES) and maternal anxiety and depression during pregnancy, and the utility of existing anxiety measurement scales during pregnancy. The preceding chapters highlight three investigations related to the aforementioned selected risk factors of PTB. Here we review the conclusions that we drew from these investigations and discuss their implications.

Main Findings, Interpretation, and Implications

Research Objective 1

The first objective of this research aimed to develop and internally validate a prediction model to examine whether neighbourhood context (specifically neighbourhood SES) along with individual maternal characteristics improves the prediction of PTB compared to a prediction model that includes maternal characteristics alone. This study found high variation in PTB attributable to neighbourhood circumstances, with neighbourhood SES explaining one quarter of the neighbourhood level variation in PTB. The model that combined neighbourhood SES along with maternal characteristics (i.e. parity, ethnicity, body mass index, smoking, depression, household income, previous PTB, and prenatal care) improved the prediction of PTB compared to the model that included maternal characteristics alone. Neighbourhood SES combined with individual level predictors had good risk stratification and modest calibration ability for identifying woman at risk for delivering a preterm infant. However, the model had high

sensitivity at the lowest risk threshold, but with a high false positive rate, and had low sensitivity at the highest risk threshold, with a low false positive rate.

This study demonstrated that knowledge of neighbourhood circumstances, including neighbourhood SES of pregnant women (in addition to their individual characteristics), can improve the discriminatory accuracy of PTB. This improved risk prediction performance indicates that, by understanding the context in which pregnant women live, healthcare providers and public health practitioners may improve their ability to identify women at increased risk of delivering preterm. This would potentially allow women and health care professionals to make more informed decisions regarding care plans. However, the prediction of PTB, by the factors considered in the present study, is suboptimal as suggested by the classification performance of the model that included both neighbourhood SES and individual level predictors. Hence, this predictive model has limited applicability in clinical or public health settings.

The model with low sensitivity at the highest risk threshold means that a substantial number of women who were at high risk for delivering preterm would be mistakenly identified as low risk. Additionally, a large proportion of women who were identified as high risk actually did not deliver preterm. While the positive predictive value was improved as the predicted risk threshold increased, ultimately it was still too low to be clinically useful. The likelihood ratio positive was improved for the highest risk threshold; however, this group only includes a few of the women who actually delivered preterm. Similarly, it has been previously demonstrated that

individual level predictors, including commonly recognized clinical risk factors, such as a history of prior PTB, or the results of clinical investigations such as short cervical length and vaginal fetal fibronectin, failed to sufficiently predict PTB (47, 126). Hence, a predictive model that better predicts PTB is yet to be identified for use in clinical or public health settings. The less optimal predictive performance for identifying the risk of PTB may be related to the complex, multiple underlying etiology of PTB and the heterogeneity between the etiology of spontaneous and iatrogenic PTB, which are different clinical entities. A combination of multiple aspects of predictors (such as biomarkers, clinical risk factors, socio-demographics, health behaviors, and neighbourhood level context), with a focus to specific type of PTB (spontaneous or iatrogenic), may adequately predict such an outcome (125, 127).

Our findings on the high variation and clustering of PTB at the neighbourhood level (with neighbourhood SES explaining some portion of this variation) reflects the presence of disparities in PTB in Alberta. This justifies the relevance of considering targeted interventions in low SES communities to reduce the risk of PTB. As such, interventions that attempt to improve neighbourhood circumstances or features (such as access to resources: healthy food, leisure or recreation center, quality health services, social support, and societal safety and security) and change population characteristics (with a focus on modifiable predictors such as smoking, inactive lifestyles, and unhealthy eating habits) may be effective in reducing the incidence of PTB.

Research Objective 2

An accurate prediction of PTB requires a valid measurement of its underlying risk factors, one of which is anxiety during pregnancy. However, most of the scales used to assess anxiety in pregnancy were validated in the general population and currently there is no well-accepted anxiety assessment scale to measure anxiety in pregnant populations. This led to the second research objective: to examine the suitability and comparability of multiple anxiety scales in pregnant women, namely the STAI-20, the STAI-6, the SCL-90, and EPDS-3A scales. The findings from this research showed various degrees of suitability of these scales in measuring anxiety during pregnancy, with the STAI-6 being adequate and the STAI-20 and the SCL-90 being inadequate. The suitability of the EPDS-3A was not able to be assessed as it contained too few items (3 items). Similarly, these scales had low to moderate correlation to each other, except the equivalency between the STAI-20 and STAI-6 scales in measuring anxiety during pregnancy. This may indicate that these scales do not measure anxiety adequately during pregnancy and that these scales are not equivalent.

Our finding indicates poor construct validity of the anxiety scales that are being used to measure anxiety during pregnancy. Particularly, these scales may conceptualize anxiety constructs differently and/or may measure constructs that are different from anxiety (60, 62, 64). The different conceptualization of anxiety constructs may arise due to multiple issues related to measuring different aspects or dimensions of anxiety, different adequacy of anxiety measurement items, and appropriateness of items (or questions asked) in measuring anxiety during pregnancy. Furthermore, the findings may entail that anxiety experienced by women

during pregnancy and anxiety experienced by the general population may differ to some extent. This means that adequate measurement of anxiety during pregnancy may require a scale that addresses both general anxiety and pregnancy-specific anxiety constructs, and by excluding one, we may miss clinically significant cases of anxiety.

Pregnancy-specific anxiety, which comprises anxiety or concerns related to giving birth, the health of infants, physical appearance, and hospitalization during and after childbirth, is, in fact, being recognized as a separate or different condition from general anxiety (64, 76). While the general anxiety scales do not include pregnancy-specific anxieties, the pregnancy-specific anxiety scales include these anxieties, but use of these scales is limited. This may be related to the unclear performance of the pregnancy-specific anxiety scales in detecting anxiety during pregnancy (64). As such, the pregnancy-specific anxiety scales do not have a reference standard tool for the criterion validation as the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for anxiety disorders does not include pregnancy-specific anxiety items.

Besides differences in the conceptualization of anxiety across these anxiety scales, use of these anxiety scales, or some of them, may lead to invalid anxiety measurement during pregnancy. Overall, inaccurate anxiety measurement during pregnancy may hinder clinical and public health practice in effectively addressing maternal mental health, and consequently, the health outcomes of their infants. Biased measurements may incorrectly label women as mentally ill and may lead to women feeling stigmatized, unnecessarily receiving further interventions, and misdirected use of resources (74, 141-143). Similarly, it may leave anxiety unrecognized and

delay further evaluation and treatment, meaning that anxiety may progress to a more severe level, which simply could have been prevented early by cost-effective interventions such as psychotherapy (74, 141-143).

As such, this research made important contributions to the literature regarding the measurement of anxiety in pregnancy, a risk factor of PTB. The observed variation in anxiety measurement across anxiety scales, in part, explains the wide variation in prevalence estimates of anxiety during pregnancy and the inconsistencies in its association with adverse pregnancy outcomes and child development in the literature (54, 57, 78-82). While the discrepancies in research findings may occur due to differences in sample characteristics and or differences in the scales used across studies, or over time, our findings support that the variation is, in part, attributable to the various anxiety scales used. This finding highlights the need for a consensus on which tools should be used to screen for and subsequently diagnose anxiety during pregnancy. As validation of existing anxiety scales in pregnant women is limited (60, 63) and no study assessed model fitness of the anxiety scales in pregnant women (except the SAI-6 scale), a thorough validation of existing anxiety scales, including content and criterion validities in addition to the construct validity, should be a first approach.

Criterion validation parameters such as sensitivity, specificity, predictive values, and likelihood ratios, identify the ability of the scale to distinguish between women who are likely to have anxiety from those who are unlikely to have anxiety, and provide a basis for selecting women who require further assessment/intervention (144-146). These results are drawn based on the

knowledge of classification accuracy and error in relation to a reference standard; thus, allows unambiguous clinically useful interpretations. Evidence-based clinical and public health practices are based on whether screening and interventions lead to better health outcomes in a defined population. This typically hinges on identifying a group of people who could benefit, or not, from a clinical assessment of their mental health. Therefore, in public health and clinical practice, it is important to classify women into higher and lower risk groups for anxiety, thereby facilitating a decision about what further assessment or intervention will lead to the best outcomes. While assessment of content and construct validity are an important part of scale development (145), they emphasize underlying theory, which is important to having a deep conceptual understanding of what is being measured by an instrument in research, unlike criterion validity, content and construct validities are not intended to guide clinical decisions. These concepts of validity do not use reference standards, are deficient in providing information about classification accuracy; thus, their results lack the unambiguous clinical interpretation of criterion-validation parameters. While we desire a simple, rapid, inexpensive, and safe anxiety screening scale in a clinical/research setting, it must be balanced with a high degree of criterion validity. Despite the importance of criterion validity in screening, its assessment is scarce in the context of anxiety scales in perinatal populations (60, 63).

Research objective 3

In addition to the validity issue around the measurement of anxiety during pregnancy, the association between anxiety during pregnancy and PTB is not well understood. Specifically, the presence of clinically significant levels of both anxiety and depression symptoms at the same

time, which likely pose higher risks in pregnancy than having anxiety or depression symptoms alone, is scarcely analyzed as a distinct risk factor for PTB. Furthermore, exposure to deprivation-associated stressors (which are common in low SES neighbourhoods) further aggravate women' emotional distress (27). Therefore, we hypothesized that neighbourhood SES may modify the association between anxiety and/or depression during pregnancy and PTB. Seeking to improve the current understanding of the associations between anxiety and depression and PTB led to the third research objective: to examine the association of anxiety symptoms alone, depression symptoms alone, and the presence of both anxiety and depression symptoms with PTB, and whether the associations differ according to neighbourhood SES of pregnant women. The study found that the presence of both anxiety and depression, but neither isolated anxiety nor depression, is associated with PTB. Women with both anxiety and depression were at high risk for delivering preterm infants and the risk was even higher if they lived in a relatively more deprived neighbourhood compared to women who lived in a less deprived neighbourhood.

The high rate of PTB among women with both anxiety and depression may relate to both the combined effects of prenatal depression and anxiety and the severity of anxiety and depression symptoms. Women with both anxiety and depression are more likely to have severe anxiety and depression symptoms**,** longer depressive episodes, worse psychosocial impairment, poor response to treatment, daily stresses, compromised quality of life, and increased suicidality than those with isolated anxiety or depression symptoms (138-140). Thus, the presence of anxiety and depression may lead to an increased risk of poor birth outcomes, including PTB,

than depression or anxiety alone. However, it also should be noted that severe symptoms of anxiety or depression during pregnancy are correlated with psychotropic medication use (such as antidepressants) which increases the risk of PTB (147, 148).

Our study found a strong association between the presence of both anxiety and depression and PTB for women living in relatively more deprived neighbourhoods. It is important to note that this finding seems to depend on an exceptionally low rate of PTB for the group of women with both anxiety and depression (who often have severe symptoms of anxiety and depression) in the least deprived neighbourhoods. Although, the replication of this finding seems important before the development of intervention strategies, this strong association supports that, besides individual-level risk factors, the risk of PTB is related to neighbourhood-level factors (22, 24, 27). To illustrate, the high rate of PTB may exist in low SES neighbourhoods because women with individual-level risk characteristics more often live in these neighbourhoods. Additionally, neighbourhood characteristics may increase the risk of PTB by exposing individuals to elevated risk or by influencing individual's ability to fulfill daily needs, access resources, make healthy lifestyle choices, and cope with different situations (22, 24, 27). For example, women living in a relatively low SES neighbourhoods often have less access to healthy foods, quality health services, opportunities for leisure activity, and social support, and have more exposure to societal stressors and crime (22, 24, 27, 28). These social disadvantages may elevate the risk of delivering PTB through biological, behavioral, and psychosocial processes.

While the exact mechanisms that anxiety, depression, and neighbourhood deprivation lead to PTB is unknown, complex multiple underlying mechanisms – comprising psychosocial and biological pathways and their interrelations – likely increase the risk of PTB (22, 28, 149-154). For example, anxiety and depression during pregnancy may lead to PTB through biological mechanisms, such as alteration of hypothalamic-pituitary-adrenal axis and inflammatory/immune activities, that results in biochemical changes in body. Similarly, anxiety and depression during pregnancy may lead to PTB through psychosocial pathways, such as adoption of unhealthy behaviors (e.g., smoking, unhealthy eating behaviors) (22, 28, 149). Comorbid depression and anxiety during pregnancy is probably the most vulnerable condition for these bio-behavioral (biological and psychosocial) mechanisms (155, 156). Additionally, people with low SES and/or living in low SES residential areas may have increased exposure to acute or chronic stressors, less access to resilience resources, high threat appraisals, and lack of control (22, 27). These exposures chronically alter the bio-behavioral stress pathways, resulting in allostatic load that may lead to the risk of PTB among those living in low SES neighbourhoods (22, 28, 149-154). Therefore, the presence of anxiety and depression together with exposure to social disadvantages (or challenges of deprivation) may provoke multiplicative effects on the risk of PTB.

This research highlights the importance of both individual and multilevel contexts of pregnant women in influencing the risk of PTB. The finding suggests that a group of women living in less advantaged areas are more likely be anxious or depressed or be both anxious and depressed compared to those living in more advantaged areas. It further suggests that a group of women

with both anxiety and depression are more likely interpret the deprivation associated stressors more acutely than those with anxiety or depression only, resulting in severe psychological distress in this group of women. This indicates that it is not always the individual level maternal characteristics, behaviors, and clinical conditions, which determine the risk of PTB. There are also contextual level or neighbourhood level factors, usually created by the social system, which increase the risk of PTB. The variation in PTB at the neighbourhood level, in fact, reflects the existence of health disparities on the risk of PTB (22, 24, 27, 28), which is potentially modifiable; thus, policy relevant. However, this research cannot claim causality between SES, including neighbourhood SES, and anxiety/depression. The causal pathway between SES and anxiety/depression is complex given their bi-directional causal relationship and additional factors such as migration.

The high risk of PTB among women with both anxiety and depression and living in low SES neighbourhoods implies that an intervention strategy that focuses on this group of women could have a large impact in reducing the incidence of PTB. However, it is important to note that co-occurrence of anxiety and depression often have severe symptoms of anxiety or depression that in fact increase the risk of PTB. This highlights the importance of identifying depressed and anxious women, as well as women who are only depressed or only experiencing anxiety, and providing support to lower their anxiety and depression levels. Furthermore, the severe symptoms of anxiety and depression are correlated with psychotropic medication use during pregnancy. While the use of antidepressant medication treats the maternal symptoms of depression, it may independently increase the risk of adverse perinatal outcomes including PTB

(147, 148, 157). Thus, developing strategies that identify and manage comorbid anxiety and depression prior to the pregnancy should be a priority.

This research highlights the importance of SES and mental health (neighbourhood, neighbourhood SES, anxiety and depression and interplay of these factors) in relation to the risk of PTB. However, the findings do not suggest that these are only the important risk factors for PTB. It is important to appreciate that PTB is a product of multiple risk factors, such as socioeconomic, behavioral, psychological and biological factors, and interconnection of these risk factors. Hence, no single intervention or practice is likely to have a major impact in reducing the rate of PTB. Prevention strategies for PTB should adopt prevention strategies targeted at high-risk individuals and at the population level. Population prevention strategies should seek to address all the factors that increase the risk of PTB and affect the entire population of women of childbearing age (158). High-risk prevention strategies that target high risk populations and modifiable risk factors such as anxiety, stress, depression, neighbourhood context, and support systems of pregnant women are also important (158).

Strengths and Limitations

This research was a collaborative multi-disciplinary project which involved various university faculties/departments, clinicians, the AOF and APrON pregnancy cohort study teams, researchers and collaborators. This collaboration ensured various perspectives in seeking to understand the psychosocial risk factors for PTB. This research utilized data from ongoing two community-based prospective pregnancy cohort studies (The AOF and the APrON) in Alberta

Canada (57, 117, 118), which were linked to neighbourhood SES data derived from the Statistics Canada census 2011. The strengths of using data from these cohort studies include: a large community-based pregnant sample or a relatively representative sample of pregnant women (compared to a hospital or clinic based sample), with a relatively low attrition rate (approximately 10% during pregnancy), and prospective measurement of exposures and outcomes (e.g., depression, anxiety, week of gestation, etc.) (57, 117, 118). The use of these cohort data provided high precision and validity to our findings, including the generalizability of the study findings.

To our knowledge, this study is the first to develop and internally validate a prediction model for PTB to investigate the ability of neighbourhood SES to predict the risk of PTB. This allowed us to understand the relevance of area of residence (in general), and more specifically area level SES, in predicting the risk of maternal health outcomes. This study used the simplest multilevel structure with individual and neighbourhood level predictors of PTB, data which can be easily collected in both community and clinical settings. This research also used a pragmatic approach, which allowed the best utilization of the cohort data. Specifically, this research analyzed anxiety data in two full cohorts and in the overlapped sample from these two cohort studies to evaluate and compare the utility of four anxiety scales in a comparable sample of pregnant women. Similarly, this study used a clinically meaningful analytical approach to examine the association between anxiety and depression during pregnancy and PTB by analyzing the association of the presence of anxiety and depression versus isolated depressive or anxious symptoms with PTB, and by further analyzing neighbourhood SES as a modifier of

this association. This approach allowed us to examine the risk of PTB across several subgroups of women with anxiety and depression and neighbourhood SES and permitted us to identify a specific group of women who may benefit the most from preventative interventions.

This research has some limitations, which should be considered while interpreting the findings. The cohorts of these two studies over-represent women with high SES in Alberta (57, 117, 118). As the importance of neighbourhood SES might be higher for those with low SES, the observed predictive ability of neighbourhood SES to PTB could have been underestimated. While this homogenous sample provided favorable conditions to compare multiple anxiety scales, it may limit the generalizability of the findings to other demographic groups. However, findings are representative to the pregnant and parenting population in urban Canada (57, 118, 129).

While the cohort datasets were rich in socio-demographic and mental health related variables and the variables were measured prospectively, the data on clinical or medical risk factors for PTB were limited. This research was not able to separate out spontaneous and iatrogenic PTB. The influence (i.e., predictive performance or association) of anxiety, depression, and SES for the risk of PTB might be stronger with a focus on spontaneous PTB. While we analyzed the association examining the influence of several potential confounders, an influence of residual confounding is likely as other confounding variables such as antidepressant use, other psychiatric conditions, and medical risk factors were not considered due to data unavailability. Approximately, 8% of total cohorts had missing data for gestational age at delivery due to their attrition from the two cohort studies. Cohort characteristics including age,

marital status, ethnicity, anxiety and depression, and socioeconomic status were similar between the groups of women who continued and discontinued the studies (117, 118). Given this, missing data on preterm birth was considered as missing completely at random although information about the gestational age at delivery or PTB status of those who discontinued the studies was unknown. Attrition bias could have occurred if the attrition depended on anxiety and depression status and PTB in a way that it differed between those who continued and discontinued the study. For example, the observed association between anxiety and depression during pregnancy and PTB would have been underestimated if the rate of PTB among those women who discontinued the study was higher because they had severe anxiety and depression than those women who continued the study. While the use of prospective measurement of depression and anxiety reduced the chance of misclassifications of anxiety and depression due to recall bias, anxiety and depression were measured using self-reported tools that threaten the validity of the measurement. Self-reported tools, specifically, the anxiety subscale of EPDS tends to provide high false-positive results (74, 75). Furthermore, the anxiety measurement scale used in this study (i.e., EPDS-3A) comprises 3 anxiety measurement items of the depression measurement scale (i.e., EPDS) and these anxiety items were not excluded from the EPDS for depression measurement. This may lead to overestimation of the co-occurrence of anxiety and depression symptoms. Additionally, some of the strata of anxiety and/or depression status by neighbourhood SES had sparse or no data on PTB. As a result, this research combined deprivation quintiles, quintile four and quintile five, which precluded our ability to observe the specific influence of each deprivation quintile. Similarly, some of the imprecise and/or insignificant estimates may have been occurred due to the few cases in some strata.

Another limitation of this research is the use of an area-based variable. This research defined neighbourhoods using the smallest geographical area in Canada (i.e., dissemination area), where people living in the smallest area are more likely to be similar for outcomes. This research used multilevel analysis that accounts for area level variation, an appropriate analytical approach for multilevel data. The model also included individual level SES, otherwise, the effect of area level SES may have been biased due to the influence of individual level SES on health outcomes. However, even doing so, we could not clarify whether individuals who live in the same area may also experience different contextual influences from many other geographical areal units. Additionally, the timing and duration in which individuals experienced these contextual influences is uncertain. Likewise, cross-sectional measurement of an area-based variables does not address social mobility that influences both individual and neighbourhood SES and consequently, health outcomes. Thus, it is hard to interpret neighbourhood influences on health outcomes, including the role of neighbourhood SES on the prediction of PTB and the interrelation of neighbourhood SES with anxiety and depression during pregnancy to increase the risk of PTB.

Application of health research findings into clinical and public health practices is important for the improvement of health outcomes or the reduction of health problems. This research internally validated a prediction model for PTB using bootstrapping. Although the observed small difference in discriminatory accuracy between the bootstrapped sample and the original sample reflected the good reproducibility of our prediction model, as the model was internally

validated, it possibly had showed artificially high performance. This suggests that the prediction model developed by this research has limited clinical applicability to use in screening for increased risk of PTB. Similarly, this study does not provide an understanding about the clinical utility or relative superiority of anxiety scales in detecting clinically significant levels of anxiety in pregnant women due to the lack of a reference standard for criterion validation. The validation of prediction model against external data is essential to understand the validity and the clinical applicability of the model. Similarly, the criterion validation of a scale against a reference standard is essential to understand the scale's clinical utility. An application of clinically useful screening tool allows the effective identification and management of the risk of PTB or the risk factors of PTB such as anxiety and depression during pregnancy; thus, potentially helping to prevent or reduce the risk of PTB.

Future Research Directions and Dissemination

This research has identified several future research directions that may further our understanding of PTB. Specifically, projects could focus on development of risk prediction models for PTB, the validation of general anxiety scales and pregnancy-specific anxiety scales, and the assessment of risk factors of PTB using life course and multilevel aspects. The application of clinically useful prediction model supports healthcare providers and public health practitioners to make informed decisions on their care by improving their ability to identify woman most at risk of delivering preterm. As a clinically useful prediction model for PTB, with a good predictive ability, has not yet been identified, continued research in this area is needed. Future research is recommended to develop a prediction model considering individual and

neighbourhood level predictors such as clinical or medical risk factors of PTB, psychosocial stressors, neighbourhood SES, social support, and societal safety and crimes, and the interrelations of these risk factors. Furthermore, external validation of the results is pertinent to improve the prediction and clinical utility.

Use of a well-conceptualized validated measurement scale would lead to optimal identification of women who would benefit from supports and services. Given the unclear utility of the existing anxiety scales in measuring anxiety during pregnancy, criterion validation of those scales (against a reference standard) in pregnant women is indispensable. The criterion validity assessment of those scales in pregnant women clarifies their ability and relative superiority in detecting clinically significant levels of anxiety during pregnancy. The criterion validation also takes into account the somatic aspects of pregnancy to further confirm the scale's value for use in pregnancy. The SAI-6 anxiety scale, the best suitable scale in measuring anxiety pregnant sample as observed by our study, has yet been evaluated against a clinical interview, which is essential before its routine adoption (as a screening tool) into clinical practice. Besides the validation of the general anxiety scales, research attention towards examining the usefulness of pregnancy-specific anxiety scales, may be needed. Future research may compare the relative utility of general anxiety scales, pregnancy-specific scales, and scales that combine both scales in pregnant population.

Psychotropic medication use is correlated with the severity of anxiety and depression, and both are linked to increased risk of PTB (108, 147, 148). Future research that examines the

association of the severity of anxiety and depression, medication use, and both (the severity of anxiety and depression and medication use) with the risk of PTB may improve the understanding of risk factors of PTB and may guide preventive strategies for PTB. Similarly, separating the risk of spontaneous and iatrogenic PTB can clarify the contribution of anxiety and depression and neighbourhood SES on PTB. Furthermore, decision makers, researchers, and care providers working in the area of PTB should be aware of that, given the multifactorial and complex nature of PTB, no single facet of research is likely to yield solutions of significant impact on PTB. Instead, many lines or aspects of research need to be considered.

The current belief is that reproductive health outcomes and chronic health problems are influenced by exposure to risk factors or protective factors over the life course (113, 154). This concept posits that the exposure to risk factors or protective factors over the life course, including at critical life periods, programs the future body functions including the body function of next generation (154). Similarly, accumulation of risk over the life course negatively affects health outcomes by increasing the allostatic load in the body (100, 154, 159). Existing studies on PTB focus on exposure to risk factors or protective factors during pregnancy and studies looking at mother's long term past experiences or exposures to health damaging and health protective factors is lacking. Cross-sectional examination of the risk or protective factors during pregnancy cannot establish causal effects between mental health or neighbourhood level factors and PTB due to several potential challenges. These challenges include reverse causation between neighbourhood circumstances and health, unmeasured confounding, residential mobility, the possibility of the same individual variable being confounder and mediator, and changes in

neighbourhood context over the life process (24, 27, 128). These factors may explain the failure of current primary and secondary prevention programs to reduce the incidence of PTB. Therefore, examination of risk of PTB using the life-course perspective, which demands longitudinal study designs with repeated measurements of psychosocial experiences and neighbourhood characteristics and outcomes over time, will be a valuable approach (24, 27, 128). Similarly, PTB has multifactorial risk factors at more than one level. This include biological biomarkers, individual's clinical characteristics, individual, family, and socio-cultural factors, psychosocial factors (stressors, resources), and contextual level factors (neighbourhood SES, crime or safety, social or community integration), and their interaction to each other. However, these factors have not been analyzed together using multilevel analysis. This type of research may identify the contribution of each etiological factors (biological, social, and psychosocial) at different level in increasing the risk of PTB; thus, has implications for policy.

Research findings have been disseminated to diverse groups of people to update knowledge and future research directions in PTB. The research findings have been submitted to peer-review journals for publication and have been shared through local, national, and international conference presentations. Additionally, the findings were shared with researchers, clinicians, decision makers, health professionals, and community agencies in Alberta through the platforms of AOF and APrON cohort studies and PolicyWise for Children and Families. Similarly, this research was presented at Alberta Children Hospital Research Institute and at a conference organized by Alberta Maternal Newborn Child and Youth Strategic Clinical Network, Alberta

Health Services, where care providers, health services researchers, program designers, and key policy makers in Alberta were present.

Conclusions

The research presented in this thesis has shown that maternal anxiety and depression during pregnancy and neighbourhood SES are important risk factors for PTB. The research findings provide insights into risk prediction of PTB, measurement of an underlying risk factor of PTB (i.e., anxiety during pregnancy), the association between anxiety and depression during pregnancy and PTB, and the interrelations between anxiety and depression and neighbourhood SES in increasing the risk of PTB. Understanding of the role of neighbourhood SES in predicting the risk of PTB may guide healthcare providers in identifying the women who are at high risk for delivering preterm and in addressing the known maternal risk factors of PTB (e.g., smoking, stress, less utilization of prenatal care, obesity, etc.), which are common in women coming from low SES areas. This also helps in addressing the neighbourhood context that itself elevates the risk of PTB. As the reduction of risk for delivering preterm infants primarily depends on effective identification of women who are likely to deliver preterm, the valid measurement of underlying risk factors for PTB is a prime essential. Understanding of the role of neighbourhood SES in the association between anxiety and depression during pregnancy and PTB may guide the identification of high-risk women for PTB and the design of population-based interventions. For example, the design of a prenatal anxiety and depression screening and counselling program that targets the reduction of anxiety and depression of vulnerable pregnant women in the low SES neighbourhood. The impact of anxiety or depression reduction interventions may

have far reaching implications that extend beyond reducing anxiety or depression during pregnancy and PTB, such as prevention of depression and anxiety during the postpartum period and their adverse consequences on mothers and babies.

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Appendix

Appendix 1: Edinburgh Postnatal Depression Scale (Anxiety Subscale includes bolded items)

As you have recently had a baby, we would like to know how you are feeling. Please UNDERLINE the answer which comes closest to how you have felt IN THE PAST 7 DAYS, not just how you feel today.

1. I have been able to laugh and see the funny side of things
    a. As much as I always could
    b. Not quite so much now
    c. Definitely not so much now
    d. Not at all

2. I have looked forward with enjoyment to things
    a. As much as I ever did
    b. Rather less than I used to
    c. Definitely less than I used to
    d. Hardly at all

3. I have blamed myself unnecessarily when things went wrong
    a. Yes, most of the time
    b. Yes, some of the time
    c. Not very often
    d. No, never

4. I have been anxious or worried for no good reason
    a. No, not at all
    b. Hardly ever
    c. Yes, sometimes
    d. Yes, very often

5. I have felt scared or panicky for no very good reason

a. Yes, quite a lot
b. Yes, sometimes
c. No, not much
d. No, not at all

6. Things have been getting on top of me

a. Yes, most of the time I haven't been able to cope at all
b. Yes, sometimes I haven't been coping as well as usual
c. No, most of the time I have coped quite well
d. No, have been coping as well as ever

7. I have been so unhappy that I have had difficulty sleeping

a. Yes, most of the time
b. Yes, sometimes
c. Not very often
d. No, not at all

8. I have felt sad or miserable

a. Yes, most of the time
b. Yes, quite often
c. Not very often
d. No, not at all

9. I have been so unhappy that I have been crying

a. Yes, most of the time
b. Yes, quite often
c. Only occasionally
d. No, never

10. The thought of harming myself has occurred to me

a. Yes, quite often
b. Sometimes
c. Hardly ever
d. Never

Appendix 2: Symptom Checklist-90-R items (Anxiety Scale items bolded)

SCL-90-R item	0 Not at all	1 A little bit	2 Moderately	3 Quite a bit	4 Extremely	How much were you distress by:
2	□	□	□	□	□	**Nervousness or shakiness inside**
6	□	□	□	□	□	Feeling critical of others
9	□	□	□	□	□	Trouble remembering things
14	□	□	□	□	□	Feeling low in energy or slowed down
17	□	□	□	□	□	**Trembling**
18	□	□	□	□	□	Feeling that most people cannot be trusted
23	□	□	□	□	□	**Suddenly scared for no reason**
24	□	□	□	□	□	Temper outbursts that you could not control
26	□	□	□	□	□	Blaming yourself for things
33	□	□	□	□	□	**Feeling fearful**
36	□	□	□	□	□	Feeling others do not understand you or are unsympathetic
38	□	□	□	□	□	Having to do things very slowly to insure correctness
39	□	□	□	□	□	**Heart pounding or racing**
41	□	□	□	□	□	Feeling inferior to others
55	□	□	□	□	□	Trouble concentrating
57	□	□	□	□	□	**Feeling tense or keyed up**
58	□	□	□	□	□	Heavy feelings in your arms or legs
61	□	□	□	□	□	Feeling uneasy when people are watching or talking about you
72	□	□	□	□	□	**Spells of terror or panic**
74	□	□	□	□	□	Getting into frequent arguments
78	□	□	□	□	□	**Feeling so restless you couldn't sit still**
79	□	□	□	□	□	Feelings of worthlessness
80	□	□	□	□	□	**The feeling that something bad is going to happen to you**
81	□	□	□	□	□	Shouting or throwing things
86	□	□	□	□	□	**Thoughts and images of a frightening nature**

Appendix 3: State Trait Anxiety Inventory- State

	Items	1 Not at all	2 A little	3 Somewhat	4 Very Much So
1	I feel calm	1	2	3	4
2	I feel secure	1	2	3	4
3	I feel tense	1	2	3	4
4	I feel strained	1	2	3	4
5	I feel at ease	1	2	3	4
6	I feel upset	1	2	3	4
7	I am presently worrying over possible misfortunes	1	2	3	4
8	I feel satisfied	1	2	3	4
9	I feel frightened	1	2	3	4
10	I feel uncomfortable	1	2	3	4
11	I feel self-confident	1	2	3	4
12	I feel nervous	1	2	3	4
13	I feel jittery	1	2	3	4
14	I feel indecisive	1	2	3	4
15	I am relaxed	1	2	3	4
16	I feel content	1	2	3	4
17	I am worried	1	2	3	4
18	I feel confused	1	2	3	4
19	I feel steady	1	2	3	4
20	I feel pleasant	1	2	3	4

Appendix 4: Model Building and Validation Strategy

A predictive model for PTB was developed using three consecutive model development steps as outlined by Merlo et al 2016 for multilevel data. These steps included development of a logistic regression model, followed by development of a multilevel logistic regression model with a random intercept, with and without including neighborhood SES. These three steps allow us to systematically develop a predictive model containing individual and neighborhood level variables.

Predictive models were developed in the bootstrapped sample (of equal size of the study sample) with 1000 replications (training dataset). A conventional multivariable logistic regression model, which included individual level variables associated with PTB ($p<0.25$), was developed using a backward variable elimination approach. Neighborhood level information was not included in this model. The individual level variable with the largest p-value was first eliminated from the full model, then, the variable with the second largest p-value was eliminated, and so on. Variables were retained in the model if the associated p-value was <0.1 or if the variable was clinically relevant. The p value <0.1 was chosen because few variables met initial criteria (in bivariate analysis) to be a potential candidate variable for full multilevel model; thus, using the liberal threshold (instead of conventional p value <0.05) would increase the chance of their retention in the model, to assess their predictive ability combining with neighborhood.

A two-level multilevel logistic regression model with a random intercept for neighborhood (DA) was developed, with 5,297 women nested into 1,501 Das; thus, on average each DA included three women. This model contained all of the individual level

predictors identified in the conventional logistic regression model. Then, the neighborhood SES variable (Pampalon material deprivation index or median personal income) was added in the multilevel logistic regression model. Different SES measures have been used across studies to measure neighborhood SES; thus, two multilevel models (one for material deprivation index and another for median personal income) were developed to explore whether the predictive ability of neighborhood SES on the risk of PTB differs by the different measures of neighborhood SES used. Multilevel models provided estimates involving the association between neighborhood SES and PTB (odds ratio (OR)) and the neighborhood variation in PTB (including intra-class correlation coefficient (ICC) and median odds ratio (MOR)). Additionally, the proportional change in variance between multilevel models with neighborhood SES and without neighborhood SES was calculated to assess the proportion of the neighborhood variance explained by neighborhood SES. The discriminative ability of three predictive models (conventional logistic regression model, multilevel logistic regression model with deprivation index, and multilevel regression model with median household income) was assessed in the bootstrapped sample and the study sample using the AUC of the receiver operating characteristic curve.

Appendix 5: Factor Loadings of Four Anxiety Scales' Individual Item

Items	Questions	Factor loading coefficient (95% CI)
Factors loadings of EPDS anxiety subscale's 3 items (AOF full cohort):		
EPDS item 3	I have blamed myself unnecessarily when things went wrong	0.58 (0.55, 0.60)
EPDS item 4	I have been anxious or worried for no good reason	0.79 (0.76, 0.82)
EPDS item 5	I have felt scared or panicky for no very good reason	0.73 (0.70, 0.76)
Factors loadings of STAI-S scale's 20 items (AOF full cohort):		
SAI item 1	I feel calm (anxiety-absent item)	0.73 (0.71, 0.75)
SAI item 2	I feel secure (anxiety-absent item)	0.66 (0.64, 0.68)
SAI item 3	I feel tense (anxiety-present item)	0.66 (0.64, 0.68)
SAI item 4	I feel regretful (anxiety-present item)	0.41 (0.38, 0.44)
SAI item 5	I feel at ease (anxiety-absent item)	0.76 (0.75, 0.78)
SAI item 6	I feel upset (anxiety-present item)	0.64 (0.62, 0.66)
SAI item 7	I feel misfortunes (anxiety-present item)	0.59 (0.56, 0.62)
SAI item 8	I feel rested (anxiety-absent item)	0.53 (0.50, 0.56)
SAI item 9	I feel anxious (anxiety-present item)	0.70 (0.68, 0.72)
SAI item 10	I feel comfortable (anxiety-absent item)	0.71 (0.69, 0.73)
SAI item 11	I feel self-confident (anxiety-absent item)	0.64 (0.62, 0.66)
SAI item 12	I feel nervous (anxiety-present item)	0.68 (0.66, 0.70)
SAI item 13	I feel jittery (anxiety-present item)	0.57 (0.55, 0.60)
SAI item 14	I feel high-strung (anxiety-present item)	0.57 (0.54, 0.59)
SAI item 15	I feel relaxed (anxiety-absent item)	0.82 (0.81, 0.83)
SAI item 16	I feel content (anxiety-absent item)	0.79 (0.78, 0.80)
SAI item 17	I feel worried (anxiety-present item)	0.70 (0.68, 0.72)
SAI item 18	I feel over-excited (anxiety-present item)	0.42 (0.39, 0.45)
SAI item 19	I feel joyful (anxiety-absent item)	0.67 (0.64, 0.69)
SAI item 20	I feel pleasant (anxiety-absent item)	0.81 (0.79, 0.82)
Factors loadings of STAI-S scale's 6 items (AOF full cohort):		

Items	Questions	Factor loading coefficient (95% CI)
SAI item1	I feel calm (anxiety-absent item)	0.76 (0.74, 0.77)
SAI item3	I feel tense (anxiety-present item)	0.73 (0.71, 0.76)
SAI item6	I feel upset (anxiety-present item)	0.65 (0.62, 0.67)
SAI item 15	I feel relaxed (anxiety-absent item)	0.86 (0.84, 0.87)
SAI item 16	I feel content (anxiety-absent item)	0.75 (0.72, 0.77)
SAI item 17	I feel worried (anxiety-present item)	0.63 (0.60. 0.65)
Factors loadings of EPDS-3A's 3 items (APrON full cohort):		
EPDS item 3	I have blamed myself unnecessarily when things went wrong	0.47 (0.43, 0.51)
EPDS item 4	I have been anxious or worried for no good reason	0.73 (0.68, 0.77)
EPDS item 5	I have felt scared or panicky for no very good reason	0.75 (0.70, 0.79)
Factors loadings of SCL-90 anxiety scale's 10 items (APrON full cohort):		
SCL item 1	Nervousness or shakiness inside	0.61 (0.58, 0.65)
SCL item 5	Trembling	0.46 (0.42, 0.51)
SCL item 7	Suddenly scared for no reason	0.71 (0.67, 0.73)
SCL item 10	Feeling fearful	0.70 (0.67, 0.73)
SCL item 13	Heart pounding or racing	0.46 (0.42, 0.51)
SCL item 16	Feeling tense or keyed up	0.57 (0.53, 0.61)
SCL item 19	Spells of terror or panic	0.66 (0.63, 0.69)
SCL item 21	Feeling so restless you couldn't sit still	0.37 (0.32, 0.42)
SCL item 23	The feeling that something bad is going to happen to you	0.67 (0.63, 0.70)
SCL item 25	Thoughts and images of a frightening nature	0.54 (0.50, 0.57)

EPDS-3A: Edinburgh postnatal depression scale anxiety scale; STAI-S: state trait anxiety inventory-state; SCL: symptom checklist; AOF: All Our Familes; APrON: Alberta Pregnancy Outcome and Nutrition; CI: confidence interval