BMJ Open

Neighborhood socioeconomic status modifies the association between anxiety and depression during pregnancy and preterm birth: A Community-based Canadian Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031035
Article Type:	Research
Date Submitted by the Author:	12-Apr-2019
Complete List of Authors:	Adhikari, Kamala; University of Calgary Cumming School of Medicine Patten, Scott Williamson, Tyler; University of Calgary Cumming School of Medicine, Community Health Sciences Patel, Alka Premji, Shahirose ; York University, Tough, Suzanne ; University of Calgary Cumming School of Medicine, Paediatrics and Community Health Science Letourneau, Nicole Giesbrecht, Gerald Metcalfe, Amy; University of Calgary, Obstetrics and Gynecology
Keywords:	MENTAL HEALTH, EPIDEMIOLOGY, Preterm birth, Neighbourhood socioeconomic status

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Neighborhood socioeconomic status modifies the association between anxiety and depression during pregnancy and preterm birth: A Community-based Canadian Cohort Study

Kamala Adhikari[1], Scott B Patten[1], Tyler Williamson[1], Alka B Patel[1,2], Shahirose Premji[3], Suzanne Tough[1,4], Nicole Letourneau[1,4,5,8], Gerald Giesbrecht[1,4], Amy Metcalfe[1,6,7]

[1]Department of Community Health Sciences, University of Calgary, Calgary, Canada; [2]Applied Research and Evaluation- Primary Health Care, Alberta Health Services, Calgary, Canada; [3]School of Nursing, Faculty of Health, York University, Calgary, Canada; [4]Department of Pediatrics, University of Calgary, Calgary, Canada; [5]Faculty of Nursing University of Calgary, Calgary, Canada; [6]Department of Obstetrics and Gynecology, University of Calgary, Calgary, Canada; [7]Department of Medicine, University of Calgary, Calgary, Canada; [8]Deprtment of Psychiatry, University of Calgary, Calgary, Canada

Corresponding author:

Kamala Adhikari

Department of Community Health Sciences, University of Calgary

3280 Hospital Drive NW, Calgary, AB, T2N 4Z6

Email: kamala.adhikaridahal@ucalgary.ca

Telephone number: 1+5870-700-7531

ORCID number: 0000-0003-2872-9496

Word Count: 3000

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 neighborhood socioeconomic status (SES) modified this association.

Methods

Individual data from two pregnancy cohort studies in Alberta, Canada (n=5,538) were linked to neighborhood 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-term of neighborhood deprivation and anxiety and/or depression.

Results

Overall, 7.3% of women delivered preterm infants. The presence of both anxiety and depression, but neither of these conditions alone, was significantly associated with PTB (OR=1.6, 95% CI=1.1, 2.3) and had significant interaction with neighborhood deprivation (p-value=0.014). The predicted probability of PTB for women with both anxiety and depression was 10.0%, which increased to 15.7% if they lived in the most deprived neighborhoods and decreased to 1.4% if they lived in the least deprived neighborhoods.

Conclusions

Effects of anxiety and depression on 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 and depression, neighborhood socioeconomic status, deprivation, preterm birth

Article summary: strengths and limitations of this study

- This study provides detail description about the relationship between anxiety and depression during pregnancy and preterm birth as it analyzed the presence of both depressive and anxious symptoms versus isolated depressive or anxious symptoms as risk factors of preterm birth, and it further examined whether neighborhood socioeconomic status modifies the relationship between these risk factors and preterm birth.
- This study used data from two community-based prospective pregnancy cohort studies. This provided an opportunity to analyze preterm birth across the several strata of anxiety, depression, and both anxiety and depression and neighborhood socioeconomic status in a relatively representative sample (compared to a hospital-based or clinic-based sample) of pregnant women.
- The study sample over-represents women from urban areas of Alberta, with high socioeconomic status, thus limiting the generalizability of the findings to urban settings.
- The use of self-reported anxiety and depression measurement scales may introduce measurement inaccuracy.

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%.(1) Preterm birth (PTB) is responsible for 35% of neonatal deaths globally.(2) 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.(3-5) Despite substantial research and interventions to prevent PTB, the incidence of PTB has not declined and its etiology remains unclear.(1, 6) Understanding the risk factors for PTB, such as psychosocial distress and neighborhood low 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.(7-10) 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.(7, 9, 10) Notably, most of the previous studies analyzed anxiety or depression without considering that they may occur in a comorbid state.(7-11) 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.(12-14) 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 neighborhood SES.(15) Neighborhood SES is an area-level measure of SES, which aggregates individual SES (such as

income, education, and employment status) at a certain geographical level.(16) Neighborhood SES may influence the risk of PTB by exposing women to health benefitting or risk elevating factors.(16-19) Low neighborhood SES may affect an individual's ability to fulfill daily needs, access resources, make lifestyle choices, and cope with different situations.(16-19) Thus, the risk of PTB that is associated with anxiety and/or depression during pregnancy may differ by neighborhood 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 neighborhood 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. (20) The description and comparability of these two cohort studies is available elsewhere,(20, 21) and justifies combining these data sources.(22) Briefly, each cohort study had similar recruitment periods (2008-2012), inclusion criteria, sampling design, and data-collection methods.(25, 26) We obtained two de-identified cohort datasets linked with neighborhood 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.

Patient and public involvement

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

Variables

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 Depression Scale (EPDS). The EDS 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).(23) The EDS has high internal consistency of 0.87,(23) a sensitivity of 78%, and specificity of 99% in the obstetric population,(24, 25) and is the most common scale used to measure antenatal and postnatal depression.(26) 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.(27) 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.(28, 29) with a sensitivity of 66.7% and specificity of 88.2% in the obstetric population.(29)The standard cut-off of ≥6 out of a maximum of 9 is used to define the presence of clinically significant anxiety during pregnancy.(29) 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 EDPS-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).

Neighborhood SES data were measured by the Pampalon material deprivation index (derived from the 2011 Statistics Canada census).(30, 31) which was aggregated at the dissemination area (DA) level. DA is the smallest geographical unit available in the Canadian census, consisting of 400-700 persons.(32) The Pampalon material deprivation index is a composite measure of neighborhood 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 neighborhoods.(30)

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 1.5% for depression to 7.5% for gestational age at delivery. Overall, 7.3% (95% CI=6.6, 8.1) of women delivered preterm infants. Women who delivered preterm infants were more likely to be non-white, obese, primiparous, and from the most deprived neighborhoods. As shown in Table 1, 17.9% of women had anxiety and/or depression: 7.7% (95% CI=7.0, 8.4) of women had both

anxiety and depression, followed by 6.0% (95% CI=5.4, 6.6) women had anxiety alone, and 4.2% (95% CI=3.7, 4.8) women had depression alone. Women with both anxiety and depression had a higher rate of PTB (10.6%, 95% CI=7.8, 14.3) compared to those with isolated anxiety (6.5%, 95% CI=4.2, 10.0) or isolated depression (8.2%, 95% CI=5.1, 12.9) or without anxiety and depression (6.9%, 95% CI=6.1, 7.7). A higher proportion of women with a presence of 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 neighborhoods ($p<0.05$) (Table 1). Mean scores of anxiety (6.6±0.4) and depression (16.2±0.13) were higher among women with both conditions compared to those with anxiety alone (6.1±0.2) or depression alone (14.6±0.12).

The presence of both anxiety and depression (adjusted odds ratio (aOR)=1.6, 95% CI=1.1, 2.3), but neither anxiety alone (aOR=0.9, 95% CI=0.5, 1.4) nor depression alone (aOR=1.3, 95% CI=0.8, 2.2), was significantly associated with PTB (Table 2). Effect modification was observed between the presence of both anxiety and depression and neighborhood SES (specifically, neighborhood 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 neighborhoods had significantly increased odds of experiencing a preterm delivery (quintile 4 and 5: aOR=2.3, 95% CI=1.3, 4.1). Whereas, compared to women without anxiety and depression, women with both anxiety and depression who lived in the least deprived neighborhood were not at elevated odds of experiencing a preterm delivery (aOR=0.2, 95 % CI=0.01, 1.3) (Table 2).

As shown in Table 3, the predicted probability of PTB for women with a presence of both anxiety and depression was 10.0% (95% CI=6.8, 13.1). It increased to 15.7% (95% CI=9.5, 22.6) if they lived in the most deprived neighborhoods – an increase of 57.1% – and it decreased to 1.4% (95% CI=0.04, 4.2) if they lived in the least deprived neighborhoods. The predicted probability of PTB for women with depression alone was 9.6% (95% CI=5.2, 14.1), which increased to 14.0% (95% CI=2.7, 25.3) if they lived in the most deprived neighborhoods. The predicted probability for women with anxiety alone and women with absence of anxiety and depression remained similar across the neighborhood deprivation indices.

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 neighborhood SES. Women with both anxiety and depression were more likely to deliver preterm infants if they lived in a relatively more deprived neighborhood compared to if they lived in a less deprived neighborhood. 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 neighborhood and it was 1% if they lived in the least deprived neighborhood. Overall, the findings suggest the importance of neighborhoods on maternal health (in general) and more specifically preterm birth.

Interpretation

Although few previous studies assessed the association between the presence of both anxiety and depression during pregnancy and PTB, our finding is consistent with their findings that the presence of both anxiety and depression increases the risk of PTB.(14, 33, 34) This may be related to the additive effects of prenatal depression and anxiety and the effects of severity of anxiety and depressive symptoms. 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.(34, 35) – the findings are consistent with our findings. 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.(12, 33, 35) 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.(14, 34) However, the finding is inconsistent with several previous studies that analyzed anxiety or depression intermixing with the presence of both conditions.(8, 10) 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 neighborhood SES, meaning that these studies averaged the association across neighborhood 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 neighborhood may reflect that, besides individual level risk factors, the risk of PTB is related to neighborhood factors.(16-18) For example, women living in deprived neighborhoods often have less access to healthy foods, quality health services, and opportunities for leisure activity, and have more exposure to societal stressors and crimes.(16-19) 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.(8, 11, 36, 37) 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 neighborhoods had 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 neighborhood 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 neighborhood 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 neighborhood 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 infants, 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,(21, 38, 39) 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 may have introduced measurement inaccuracy. Specifically, the EPDS-3A tends to provide high false-positive results. (28, 29) 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 neighborhoods compared to women living in high SES neighborhoods. 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 neighborhood 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.

Authors contributions

Kamala Adhikari involved in the conception and design of the study. Kamala is also responsible for conducting the analysis, interpreting the data, and drafting the manuscript. 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 manuscript. Scott Patten, Tyler Williamson, Alka B Patel, Shahirose Premji, Suzanne Tough, Nicole Letourneau, and Gerald Giesbrecht were involved in the conception and design of the study and provided interpretation and intellectual content to subsequent drafts of the manuscript. All authors read and approved the final draft.

Acknowledgements

Kamala Adhikari was awarded the Vanier Canada Graduate Scholarship and the Alberta Innovates Graduate Studentship Award. Amy Metcalfe is supported by a Canadian Institutes of Health Research New Investigator Award. We acknowledge the All Our Families and the Alberta Pregnancy Outcomes and Nutrition cohort study teams for providing permission to use their data. We acknowledge SAGE (Secondary Analysis to Generate Evidence), the secure data repository developed by PolicyWise for Children and Families, which houses these datasets, for providing access to these datasets.

Role of funding agency

Kamala Adhikari was awarded the Vanier Canada Graduate Scholarship (Award code: 201611CGV-382013-267341) by the Canadian Institutes of Health Research and the Alberta Innovates Graduate Studentship Award (Award code: 201611CGV-382013-267341) by the

Alberta Innovates to conduct this study. The funding agencies have no role in study design, data access, analysis, and interpretation, manuscript writing, and in the decision to submit the article for publication.

Data sharing

Additional data such as statistical codes, supplementary tables, and technical appendix are available upon request (by emailing Kamala Adhikari: kamala.adhikaridahal@ucalgary.ca)

Ethical statements

Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary (REB16-2548_REN1). This study used secondary data and all the data were anonymized; therefore, did not require informed consent.

Competing interests

The authors declare that they have no competing interests.

References

1. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012;379(9832):2162-72.

2. Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet* 2012;379(9832):2151-61.

3. Johnston KM, Gooch K, Korol E, et al. The economic burden of prematurity in Canada. *BMC Pediatr* 2014;14:93.

4. Blencowe H, Cousens S, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. *Reprod Health* 2013;10 Suppl 1:S2.

5. Ward RM, Beachy JC. Neonatal complications following preterm birth. *Bjog* 2003;110 Suppl 20:8-16.

6. Canadian Institute for Health Information. CIHI Snapshot: Inpatient Hospitalizations, Surgeries, Newborns and Childbirth Indicators. Canadian Institute of Health Information (www.cihi.ca) 2016. Accessed on February 2019.

7. Ding XX, Wu YL, Xu SJ, et al. Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. *J Affect Disord* 2014;159:103-10.

8. Grote NK, Bridge JA, Gavin AR, et al. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch Gen Psychiatry* 2010;67(10):1012-24.

9. Staneva A, Bogossian F, Pritchard M, et al. The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: A systematic review. *Women Birth* 2015;28(3):179-93.

10. Rose MS, Pana G, Premji S. Prenatal Maternal Anxiety as a Risk Factor for Preterm Birth and the Effects of Heterogeneity on This Relationship: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2016;2016:8312158.

11. Alder J, Fink N, Bitzer J, et al. Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? A critical review of the literature. *J Matern Fetal Neonatal Med* 2007;20(3):189-209.

12. Misri S, Swift E. Generalized Anxiety Disorder and Major Depressive Disorder in Pregnant and Postpartum Women: Maternal Quality of Life and Treatment Outcomes. *J Obstet Gynaecol Can* 2015;37(9):798-803.

13. Wenzel A, Haugen EN, Jackson LC, et al. Anxiety symptoms and disorders at eight weeks postpartum. *J Anxiety Disord* 2005;19(3):295-311.

14. Field T, Diego M, Hernandez-Reif M, et al. Comorbid depression and anxiety effects on pregnancy and neonatal outcome. *Infant Behav Dev* 2010;33(1):23-9.

15. Yang S, Kestens Y, Dahhou M, et al. Neighborhood deprivation and maternal psychological distress during pregnancy: a multilevel analysis. *Matern Child Health J* 2015;19(5):1142-51.

16. Berkman LA, Kawachi I. Neighborhood and Health. New York: Oxford University Press Inc. 2003.

17. Diez Roux AV, Mair C. Neighborhoods and health. *Ann N Y Acad Sci* 2010;1186:125-45.

18. Lynch JW, Kaplan GA. Socioeconomic Factors. In: Berkman LF and Karachi I (eds.). Social Epidemiology. New York: Oxford University Press 2000.

19. Dunkel Schetter C. Psychological science on pregnancy: stress processes, biopsychosocial models, and emerging research issues. *Annu Rev Psychol* 2011;62:531-58.

20. Kaplan BJ, Giesbrecht GF, Leung BM, et al. The Alberta Pregnancy Outcomes and Nutrition (APrON) cohort study: rationale and methods. *Matern Child Nutr* 2014;10(1):44-60.

21. Leung BM, McDonald SW, Kaplan BJ, et al. Comparison of sample characteristics in two pregnancy cohorts: community-based versus population-based recruitment methods. *BMC Med Res Methodol* 2013;13:149.

22. Roberts GBD. Analyses Based on Combining Similar Information from Multiple Surveys. Section on Survey Research Methods Joint Statistical Meetings (JSM); 2009. p. 2138-47.

23. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987;150:782-6.

24. Rubertsson C, Borjesson K, Berglund A, et al. The Swedish validation of Edinburgh Postnatal Depression Scale (EPDS) during pregnancy. *Nord J Psychiatry* 2011;65(6):414-8.

25. Beck CT, Gable RK. Comparative analysis of the performance of the Postpartum Depression Screening Scale with two other depression instruments. *Nurs Res* 2001;50(4):242-50.

26. Boyd RC, Le HN, Somberg R. Review of screening instruments for postpartum depression. *Arch Womens Ment Health* 2005;8(3):141-53.

27. Gaynes BN, Gavin N, Meltzer-Brody S, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. *Evid Rep Technol Assess (Summ)* 2005(119):1-8.

28. Matthey S, Fisher J, Rowe H. Using the Edinburgh postnatal depression scale to screen for anxiety disorders: conceptual and methodological considerations. *J Affect Disord* 2013;146(2):224-30.

29. Matthey S. Using the Edinburgh Postnatal Depression Scale to screen for anxiety disorders. *Depress Anxiety* 2008;25(11):926-31.

30. Pampalon R, Raymond G. A deprivation index for health and welfare planning in Quebec. *Chronic Dis Can* 2000;21(3):104-13.

31. Alberta Health Services. How to use the Pampalon Deprivation Index in Alberta. *Research and Innovation, Alberta Health Services* 2016.

32. Canadian Institute for Health Information. Reducing gaps in Health: A focus on socioeconomic status in Urban Canada. Ottawa, Ont. Canadian Institute for Health Information 2008.

33. Flynn HA, McBride N, Cely A, et al. Relationship of prenatal depression and comorbidities to infant outcomes. *CNS Spectr* 2015;20(1):20-8.

34. Ibanez G, Charles MA, Forhan A, et al. Depression and anxiety in women during pregnancy and neonatal outcome: data from the EDEN mother-child cohort. *Early Hum Dev* 2012;88(8):643-9.

35. Pollack MH. Comorbid anxiety and depression. *J Clin Psychiatry* 2005;66 Suppl 8:22-9.

36. Kessler RC. Stress, social status, and psychological distress. *J Health Soc Behav* 1979;20(3):259-72.

37. Seguin L, Potvin L, St-Denis M, et al. Chronic stressors, social support, and depression during pregnancy. *Obstet Gynecol* 1995;85(4):583-9.

38. McDonald SW, Lyon AW, Benzies KM, et al. The All Our Babies pregnancy cohort: design, methods, and participant characteristics. *BMC Pregnancy Childbirth* 2013;13 Suppl 1:S2.

39. Gracie SK, Lyon AW, Kehler HL, et al. All Our Babies Cohort Study: recruitment of a cohort to predict women at risk of preterm birth through the examination of gene expression profiles and the environment. *BMC Pregnancy Childbirth* 2010;10:87.

Table 1: Distribution of maternal characteristics across anxiety and depression status during pregnancy

Maternal characteristics	Absence of both anxiety and depression n=4294 (82.1%)	Presence of anxiety only n=312 (6.0%)	Presence of depression only n=220 (4.2%)	Presence of both anxiety and depression n=402 (7.7%)	$\chi 2$ p-value
	n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)	
Maternal age					0.006
≥35yrs	886 (21.0, 19.8-22.3)	48 (15.5, 11.9-22.0)	59 (27.4, 21.9-33.8)	71 (18.4, 14.8-22.6)	
Marital status					
Single/divorced/separated	168 (3.9, 3.4-4.6)	22 (7.2, 4.8-10.7)	25 (11.5, 7.9-16.4)	47 (11.8, 8.9-15.4)	<0.0001
Ethnicity					<0.0001
Non-white	807 (19.0, 17.9-20.2)	68 (22.2, 17.8-27.1)	67 (30.9, 25.1-37.3)	143 (36.1, 31.5-40.9)	
Duration of stay in Canada					<0.0001
Born/5 years+	3841 (91.6, 90.7-92.4)	275 (89.9, 85.9-92.8)	185 (87.3, 82.1-91.1)	329 (84.4, 80.4-87.6)	
<5 years	352 (8.4, 7.6-9.3)	31 (10.1, 7.2-14.1)	27 (12.7, 8.9-17.9)	61 (15.6, 12.4-19.6)	
Body mass index					0.002
Underweight (<18.5kg/m^2)	170 (4.2, 3.6-4.9)	12 (4.1, 2.3-7.1)	11 (5.3, 2.9-9.3)	21 (5.6, 3.7-8.4)	
Normal weight (18.5 - 24.99 kg/m^2)	2552 (63.2, 61.7-64.7)	172 (58.5, 52.8-64.0)	125 (59.8, 53.0-66.2)	220 (58.4, 53.3-63.2)	
Overweight (25 - 29.99 kg/m^2)	882 (21.9, 20.6-23.1)	59 (20.1, 15.9-25.0)	50 (23.9, 18.6-30.2)	73 (19.4, 15.7-23.7)	
Obesity (≥30 kg/m^2)	432 (10.7, 9.8-11.7)	51 (17.4, 13.4-22.1)	23 (11.0, 7.4-16.0)	63 (16.7,13.3-20.8)	
Parity					<0.0001
Primiparous	2106 (49.7, 48.2-51.2)	109 (35.4, 30.2-40.9)	111 (51.2, 44.5-57.7)	190 (48.1, 43.2-53.0)	
Unintended pregnancy	742 (17.4, 16.3-18.6)	70 (22.6, 18.3-27.6)	72 (32.9, 27.0-39.4)	122 (30.7, 26.3-35.4)	<0.0001
Smoked before pregnancy	822 (19.3, 18.2-20.6)	86 (27.9, 23.2-33.2)	61 (28.0, 22.4-34.3)	123 (30.9, 26.56-4.6)	<0.0001
Alcohol consumption before pregnancy	3603 (84.7, 83.6-85.8)	268 (87.0, 82.8-90.3)	181 (82.7, 77.1-87.1)	305 (76.6, 72.2-80.5)	<0.0001
Drug abuse before pregnancy	561 (13.2, 12.2-14.2)	61 (19.9, 15.8-24.7)	44 (20.4, 15.5-26.3)	83 (20.8, 17.1-25.1)	<0.0001
Maternal education					<0.0001
High school or less than high school	451 (10.6, 9.7-11.6)	49 (16.2, 12.5-20.8)	42 (19.4, 14.7-25.3)	68 (17.3, 13.9-21.4)	
Some post-secondary	669 (15.8, 14.7-16.9)	57 (18.9, 14.8-23.7)	35 (16.2, 11.9-21.7)	96 (24.4, 20.4-28.9)	
Completed post-secondary	3121 (73.6, 72.2-74.9)	196 (64.9, 59.4-70.1)	139 (64.4, 57.7-70.5)	229 (58.3,53.3-63.1)	

Maternal characteristics	Absence of both anxiety and depression n=4294 (82.1%)	Presence of anxiety only n=312 (6.0%)	Presence of depression only n=220 (4.2%)	Presence of both anxiety and depression n=402 (7.7%)	$\chi 2$ p-value
	n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)	
Household income					<0.0001
<$40,000	325 (7.8, 7.1-8.7)	25 (8.4, 5.7-12.1)	40 (18.6, 13.9-24.4)	85 (22.0, 18.2-26.4)	
$40,000 - <$70,000	542 (13.0, 12.8-14.1)	53 (17.8, 13.8-22.6)	43 (20.0, 15.9-25.9)	83 (21.5, 17.7-25.7)	
$70,000 - <$100,000	989 (23.8, 22.5-25.1)	76 (25.5, 20.9-30.8)	52 (24.2, 18.9-30.4)	85 (22.0, 18.2-26.4)	
≥$100,000	2301 (55.4, 53.8-56.9)	144 (48.3, 42.7-54.0)	80 (37.2, 31.0-43.9)	133 (34.5, 29.9-39.3)	
Inadequate social support anytime during pregnancy	731 (17.1, 16.0-18.3)	77 (25.0, 20.5-30.1)	127 (57.4, 51.3-64.4)	210 (52.4, 47.5-57.2)	<0.0001
Neighborhood deprivation index					<0.0001
Quintile 1 (least deprived)	1108 (27.7, 26.3-29.1)	68 (24.3, 19.6-29.7)	51 (24.9, 19.4-31.3)	80 (22.4, 18.3-26.9)	
Quintile 2	1045 (26.1, 24.8-27.5)	82 (29.3, 24.3-34.9)	41 (20.0, 15.1-26.0)	83 (23.2, 19.1-27.8)	
Quintile 3	800 (20.0, 18.8-21.3)	64 (22.9, 18.3-28.1)	39 (19.0, 14.2-24.9)	65 (18.2, 14.5-22.5)	
Quintile 4	618 (15.5, 14.4-16.6)	37 (13.2, 9.7-17.7)	30 (14.6, 10.4-20.2)	47 (13.1,10.0-17.0)	
Quintile 5 (most deprived)	429 (10.7, 9.8-11.7)	29 (10.4, 7.3-14.5)	44 (21.5, 16.4-27.6)	83 (23.2,19.1-27.8)	
Preterm birth	276 (6.9, 6.1-7.7)	19 (6.5, 4.2-10.0)	16 (8.2, 5.1-12.9)	37 (10.6, 7.8-14.3)	0.068

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

Table 2: 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 neighborhood 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	0.9 (0.5-1.4)	0.6 (0.2-1.9)	0.72 (0.3-2.1)	1.1 (0.4-3.0)	1.0 (0.4-2.8)
Presence of depression only	1.3 (0.8-2.2)	0.6 (0.18-2.0)	0.9 (0.2-3.8)	1.9 (0.8-6.6)	2.7 (0.9-7.3)
Presence of both anxiety and depression	1.6 (1.1-2.3)	0.2 (0.02-1.3)	1.4 (0.6-3.4)	2.7 (1.3-6.1)	2.3 (1.3-4.1)

[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 neighborhood; [d]quintile 5: most deprived neighborhood (quintile 4 and 5 were combined due to few or no cases in some strata); OR: odds ratio; CI: confidence interval

Table 3: Predicted marginal prevalence of preterm birth[a]

Anxiety and depression status during pregnancy[b]	Overall % (95%CI)	Stratified by neighborhood 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	7.1 (6.8-13.1)	7.6 (5.6-9.3)	6.4 (4.8-7.9)	6.9 (5.06-8.8)	7.6 (5.9-9.3)
Presence of anxiety only	6.3 (3.3-9.1)	5.4 (0.2-10.7)	4.9 (0.3-9.5)	6.5 (0.34-12.7)	7.9 (1.3-14.6)
Presence of depression only	9.6 (5.2-14.1)	4.7 (0.5-10.4)	5.7 (0.45-13.4)	13.3 (3.4-23.2)	14.0 (2.7-25.3)
Presence of both anxiety and depression	10.0 (6.8-13.1)	1.4 (0.04-4.2)	8.0 (1.9-14.1)	15.9 (6.3-25.6)	15.7 (9.5-22.6)

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

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4, and 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6 and 7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7 and 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7 and 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9, 10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9, 10
Bias	9	Describe any efforts to address potential sources of bias	8, 9, 10
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9, 10
		(*b*) Describe any methods used to examine subgroups and interactions	9, 10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Not provided now: can be provided if requested
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, 11, 12, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	10, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11, Table 2 and 3
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not done
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11 and Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13, 14, 15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17, 18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Neighborhood socioeconomic status modifies the association between anxiety and depression during pregnancy and preterm birth: A Community-based Canadian Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031035.R1
Article Type:	Original research
Date Submitted by the Author:	11-Nov-2019
Complete List of Authors:	Adhikari, Kamala; University of Calgary Cumming School of Medicine Patten, Scott Williamson, Tyler; University of Calgary Cumming School of Medicine, Community Health Sciences Patel, Alka Premji, Shahirose ; York University, Tough, Suzanne ; University of Calgary Cumming School of Medicine, Paediatrics and Community Health Science Letourneau, Nicole Giesbrecht, Gerald Metcalfe, Amy; University of Calgary, Obstetrics and Gynecology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Obstetrics and gynaecology, Public health
Keywords:	MENTAL HEALTH, EPIDEMIOLOGY, Preterm birth, Neighbourhood socioeconomic status

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Neighborhood socioeconomic status modifies the association between anxiety and depression during pregnancy and preterm birth: A Community-based Canadian Cohort Study

Kamala Adhikari[1], Scott B Patten[1], Tyler Williamson[1], Alka B Patel[1,2], Shahirose Premji[3], Suzanne Tough[1,4], Nicole Letourneau[1,4,5,8], Gerald Giesbrecht[1,4], Amy Metcalfe[1,6,7]

[1]Department of Community Health Sciences, University of Calgary, Calgary, Canada; [2]Applied Research and Evaluation- Primary Health Care, Alberta Health Services, Calgary, Canada; [3]School of Nursing, Faculty of Health, York University, Calgary, Canada; [4]Department of Pediatrics, University of Calgary, Calgary, Canada; [5]Faculty of Nursing University of Calgary, Calgary, Canada; [6]Department of Obstetrics and Gynecology, University of Calgary, Calgary, Canada; [7]Department of Medicine, University of Calgary, Calgary, Canada; [8]Deprtment of Psychiatry, University of Calgary, Calgary, Canada

Corresponding author:

Kamala Adhikari

Department of Community Health Sciences, University of Calgary

3280 Hospital Drive NW, Calgary, AB, T2N 4Z6

Email: kamala.adhikaridahal@ucalgary.ca

Telephone number: 1+5870-700-7531

ORCID number: 0000-0003-2872-9496

Word Count: 3604

Abstract

Objective: This study examined the association of anxiety alone, depression alone, and the presence of both anxiety and depression with PTB and further examined whether neighborhood socioeconomic status (SES) modified this association.

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 neighborhood SES data from the 2011 Canadian census.

Setting: Calgary, Alberta, Canada

Participants: Overall, 5,538 pregnant women who were <27 weeks of gestation and >15 years old were enrolled in the cohort studies between 2008 and 2012. 3,341 women participated in the AOF study and 2,187 women participated in the APrON study, with 231 women participated in both studies. Women who participated in both studies were only counted once.

Primary and secondary outcome measures: PTB was defined as delivery prior to 37 weeks of gestation. 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.

Results: Overall, 7.3% of women delivered preterm infants. The presence of both anxiety and depression, but neither of these conditions alone, was significantly associated with PTB

(OR=1.6, 95% CI=1.1, 2.3) and had significant interaction with neighborhood deprivation (p-value=0.004). The predicted probability of PTB for women with both anxiety and depression was 10.0%, which increased to 15.7% if they lived in the most deprived neighborhoods and decreased to 1.4% if they lived in the least deprived neighborhoods.

Conclusions: Effects of anxiety and depression on 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 and depression, neighborhood socioeconomic status, deprivation, preterm birth

Article summary: strengths and limitations of this study

- This study used data from two community-based prospective pregnancy cohort studies that were conducted in a relatively representative sample (compared to a hospital-based or clinic-based sample) of pregnant women.
- This study performed detail analysis about the relationship between anxiety and depression during pregnancy and preterm birth by examining the presence of both depressive and anxious symptoms versus isolated depressive or anxious symptoms as risk factors of preterm birth, and further examining whether neighborhood socioeconomic status modifies the relationship.
- This study analyzed overall preterm birth as data on spontaneous and iatrogenic preterm birth were not available.
- The study sample over-represents women from urban areas of Alberta, with high socioeconomic status, thus limiting the generalizability of the findings to urban settings.
- The use of self-reported anxiety and depression measurement scales may introduce measurement inaccuracy.

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%.(1) Preterm birth (PTB) is responsible for 35% of neonatal deaths globally.(2) 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.(3-5) Despite substantial research and interventions to prevent PTB, the incidence of PTB has not declined and its etiology remains unclear.(1, 6) Understanding the risk factors for PTB, such as psychosocial distress and neighborhood low 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.(7-10) 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.(7, 9, 10) Notably, most of the previous studies analyzed anxiety or depression without considering that they may occur in a comorbid state.(7-11) 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.(12-14) 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 neighborhood SES.(15) Neighborhood SES is an area-level measure of SES, which aggregates individual SES (such as

income, education, and employment status) at a certain geographical level.(16) Neighborhood SES may influence the risk of PTB by exposing women to health benefitting or risk elevating factors, such as access to healthy foods, quality health services, opportunities for leisure activity, and social support and exposure to societal stressors, crimes, and poor air and water quality.(16-19) Low neighborhood SES may affect an individual's ability to fulfill daily needs, access resources, make lifestyle choices, and cope with different situations.(16-19) Thus, the risk of PTB that is associated with anxiety and/or depression during pregnancy may differ by neighborhood 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 neighborhood 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. The description and comparability of these two cohort studies is available elsewhere,(20, 21) and justifies combining these data sources.(22) The AOF study aimed to examine maternal well-being and infant outcomes and the APrON study aimed to investigate the role of prenatal maternal nutrition

on maternal mental health and infant outcomes.(20, 21) Briefly, each cohort study had similar inclusion criteria, sampling design (community-based, non-stratified sampling), and data collection methods.(21) Both studies recruited pregnancy cohorts between 2008 and 2012 from maternity clinics, high schools, public places, etc. and followed them up. The follow-up for mother and child dyad is still ongoing in both studies.(21)

We obtained two de-identified cohort datasets linked with neighborhood 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.

Patient and public involvement

This study used de-identified secondary data. Patient and public were not involved in the design or planning of the study.

Variables

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. Data on age, ethnicity (white includes all Caucasians and non-white includes all non-Caucasians), maternal SES, parity, BMI, smoking status, social support, depression, and anxiety were collected at <27 weeks of gestation (in the APrON study) and at <25 weeks of gestation (in the AOF study). BMI was calculated based on the self-reported pre-pregnancy height and weight (i.e., immediately before pregnancy). Additionally, depression and anxiety were measured during the third trimester (APrON: 27-42 weeks of gestation; AOF: 34-36 weeks of gestation).(20, 21)

Both cohorts used an identical measure of depression, i.e., the Edinburgh 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).(23) The EPDS has high internal consistency of 0.87,(23) a sensitivity of 78%, and specificity of 99% in the obstetric population,(24, 25) and is the most common scale used to measure antenatal and postnatal depression.(26) 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.(27) 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 by previous studies,(28, 29) with a sensitivity of 66.7% and specificity of 88.2% in the obstetric population.(29)The standard cut-off of ≥6 out of a maximum of 9 is used to define the presence of clinically significant anxiety during pregnancy.(29) 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 EDPS-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 isolated anxiety or depression was defined as meeting the anxiety or depression definition during pregnancy. Presence of both anxiety and depression was defined as meeting both anxiety and depression definitions at the same time point in pregnancy. Births that occurred before 37 weeks of gestation were defined as PTB (both spontaneous and iatrogenic included). PTB was measured at 4 months of postpartum period based on maternal recall of week of gestation at delivery.

Neighborhood SES data were measured by the Pampalon material deprivation index (derived from the 2011 Statistics Canada census)(30, 31) which was aggregated at the dissemination area (DA) level. DA is the smallest geographical unit available in the Canadian census, consisting of 400-700 persons.(32) The Pampalon material deprivation index is a

composite measure of neighborhood 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 deprivation quintile, with quintile 1 representing the least deprived and quintile 5 representing the most deprived neighborhoods.(30) Neighborhood SES was assigned to each cohort based on their postal code of residence at the time of cohort recruitment.

Data Analysis

First, variables significantly associated with PTB as well as anxiety and/or depression ("anxiety only," "depression only," and "both anxiety and depression") were identified using bivariate analysis ($p<0.05$). The significantly associated variables were parity, ethnicity, and body mass index. Then, a multivariable logistic regression model was constructed to examine the association between anxiety and/or depression and PTB, adjusting for parity, ethnicity, and body mass index. Smoking, social support, and maternal education and household income variables were also initially selected based on literature to include in the multivariable model, considering that they may change or confound the association between anxiety/depression and PTB in the multivariable model. However, these variables did not change or confound the association in the multivariable model and were thus dropped from the model.

A multilevel multivariable logistic regression model, which assumes the lack of independence of observations and accounts for the variation between groups or areas, was then constructed to examine the effect modification of neighborhood SES on the association between anxiety and/or depression and PTB. This model included interaction terms in addition to parity, ethnicity, and body mass index. The interaction terms comprised "anxiety only," "depression only," and "both anxiety and depression" combined with each quintile of deprivation indices. Deprivation quintile 4th and 5th 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. 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. Alpha (α) of <0.05 was used to determine statistical significance. All analyses were performed using STATA/IC 14.1.

Missing Data

The proportion of missing data for gestational age at delivery (PTB) was 7.5%, for neighborhood deprivation indices was 7.8%, and for body mass index was 6.8%. Other variables had missing data <5%, ranging from 1.3% for depression to 4.4% for household total income. The missing data for these variables occurred due to maternal non-response. Characteristics of groups of women (such as ethnicity, parity, BMI, neighborhood SES, anxiety and depression) with and without missing data on PTB were compared to assess differences. Multiple imputation was used to address with missing data on the three variables (i.e., PTB , body mass index, and neighborhood deprivation indices) that had ≥5% missing data .(33) Using STATA's "mi Package", the multiple imputation process was carried out in three steps as recommended by Rubin: imputation, analysis, and combination.(33, 34) The method assumes that the missing data are missing at random and attempts to estimate a missing value within a plausible set of values.(33, 34) The imputation values (i.e., a predictive distribution based on observed data) were estimated using an imputation model (with imputation 50 times).(33, 34) The imputation model included the variables that were significant with missing data (i.e., marital status, duration

of stay in Canada, maternal education, and household total income, intended pregnancy, smoking, alcohol consumption) as well as those that were utilized in the analysis model (i.e., PTB, ethnicity, parity, BMI, neighborhood SES, anxiety and depression, and interaction terms). Sensitivity analysis was done to compare the estimates from the analyses based on multiple imputation and from the analysis restricted to complete case.

RESULTS

Of total 5,297 pregnant women, 17.9% of women had anxiety and/or depression: 7.7% of women had both anxiety and depression, followed by 6.0% women had anxiety alone, and 4.2% women had depression alone. Women with both anxiety and depression had a higher rate of PTB (10.6%) compared to those with isolated anxiety (6.5%) or isolated depression (8.2%) or without anxiety and depression (6.9%). A higher proportion of women with a presence of 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 neighborhoods ($p<0.05$) (Table 1). Mean scores of anxiety (mean=6.6, standard deviation (SD)=0.4) and depression (mean=16.2, SD=0.13) were higher among women with both conditions compared to those with anxiety alone (mean=6.1, SD=0.2) or depression alone (mean=14.6, SD=0.12). As shown in Table 2, women who delivered preterm infants were more likely to be non-white, obese, primiparous, and from the most deprived neighborhoods. Maternal ethnicity, parity, BMI, neighborhood SES, anxiety, and depression were significantly associated with the presence of missing data on PTB.

The presence of both anxiety and depression (adjusted odds ratio (aOR)=1.6, 95% CI=1.1, 2.3), but neither anxiety alone (aOR=0.8, 95% CI=0.5, 1.4) nor depression alone

(aOR=1.3, 95% CI=0.8, 2.3), was significantly associated with PTB (Table 3). Effect modification was observed between the presence of both anxiety and depression and neighborhood SES (p-value=0.004). Compared to women without anxiety and depression, women with both anxiety and depression who lived in quintile 3 and more deprived neighborhoods had significantly increased odds of experiencing a preterm delivery (quintile 4 and 5: aOR=2.2, 95% CI=1.3, 3.9). In contrast, compared to women without anxiety and depression, women with both anxiety and depression who lived in the least deprived neighborhood were not at elevated odds of experiencing a preterm delivery (aOR=0.2, 95 % CI=0.1, 1.5) (Table 3). The OR estimates from the analyses based on multiple imputation and from the analysis restricted to complete cases were similar, with some confidence intervals being slightly narrower in the multiple imputation analysis.

As shown in Table 4, the predicted probability of PTB for women with a presence of both anxiety and depression was 10.0% (95% CI=6.8, 13.1). It increased to 15.7% (95% CI=9.5, 22.6) if they lived in the most deprived neighborhoods – an increase of 57.1% – and it decreased to 1.4% (95% CI=0.1, 4.2) if they lived in the least deprived neighborhoods. The predicted probability of PTB for women with depression alone was 9.6% (95% CI=5.2, 14.1), which increased to 14.0% (95% CI=2.7, 25.3) if they lived in the most deprived neighborhoods. The predicted probability for women with anxiety alone and women with absence of anxiety and depression remained similar across the neighborhood deprivation indices.

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 neighborhood SES. Women with both anxiety and depression were more likely to deliver preterm infants if they lived in a relatively more deprived neighborhood compared to if they lived in a less deprived neighborhood. 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 neighborhood and it was 1% if they lived in the least deprived neighborhood. Overall, the findings suggest the importance of neighborhoods on maternal health (in general) and more specifically preterm birth.

Interpretation

Although few previous studies assessed the association between the presence of both anxiety and depression during pregnancy and PTB, our finding is consistent with their findings that the presence of both anxiety and depression increases the likelihood of PTB.(14, 35, 36) This may be related to the additive effects of prenatal depression and anxiety and the effects of severity of anxiety and depressive symptoms. 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.(36, 37). 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.(12, 35, 37) Thus, the presence of both anxiety and depression during pregnancy may

lead to an increased risk of poor birth outcomes, including PTB, relative to depression or anxiety alone.

Our study did not find an association between anxiety alone or depression alone and PTB, which is consistent with a previous pregnancy cohort study that analyzed isolated anxiety or depression separately from the presence of both or comorbid anxiety and depression.(36) However, the finding is inconsistent with several previous studies that analyzed anxiety or depression intermixing with the presence of both conditions.(8, 10) 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 neighborhood SES, meaning that these studies averaged the association across neighborhood 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 neighborhood may reflect that, besides individual level risk factors, PTB is related to neighborhood factors.(16-18) For example, women living in deprived neighborhoods often have less access to healthy foods, quality health services, and opportunities for leisure activity, and have more exposure to societal stressors and crimes.(16-19) 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.(8, 11, 38, 39) 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 neighborhoods 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 neighborhood 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 neighborhood 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 neighborhood 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 infants, 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,(21, 40, 41) 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 may have introduced measurement inaccuracy. Specifically, the EPDS-3A scale has not been validated in a pregnant population and it tends to provide high false-positive results based on its validation on during the postpartum period.(28, 29) 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 since they were not available in the study's data sources. Similarly, we were not able to separate out spontaneous and iatrogenic PTB in the model – the association might be stronger for spontaneous PTB. Overall, replication of this study addressing these limitations may further the understanding on risk factors and preventive strategies of PTB.

We defined neighborhoods using the smallest area (i.e., dissemination area) where people living in the smallest area are more likely to be similar for the outcomes, used multilevel analysis that accounts for area-level variation, and adjusted for individual level variables, an appropriate analytical approach for multilevel data. However, it is difficult to interpret the influence of

neighborhood SES using area-based variables, where women living in the same area share the same value for the variable. 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.

Conclusions

Our study found that the presence of both prenatal anxiety and depression increases the likelihood of PTB and the effect of this combination is stronger for women living in low SES neighborhoods compared to women living in high SES neighborhoods. The finding may help to inform development of intervention strategies (such as timely screening and management of anxiety and depression) that focus on the most deprived neighborhood. 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.

Authors contributions

Kamala Adhikari involved in the conception and design of the study. Kamala is also responsible for conducting the analysis, interpreting the data, and drafting the manuscript. 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 manuscript. Scott Patten, Tyler Williamson, Alka B Patel, Shahirose Premji, Suzanne Tough, Nicole Letourneau, and Gerald Giesbrecht were involved in the conception and design of the study and provided interpretation and intellectual content to subsequent drafts of the manuscript. All authors read and approved the final draft.

Acknowledgements

Kamala Adhikari was awarded the Vanier Canada Graduate Scholarship and the Alberta Innovates Graduate Studentship Award. Amy Metcalfe is supported by a Canadian Institutes of Health Research New Investigator Award. We acknowledge the All Our Families and the Alberta Pregnancy Outcomes and Nutrition cohort study teams for providing permission to use their data. We acknowledge SAGE (Secondary Analysis to Generate Evidence), the secure data repository developed by PolicyWise for Children and Families, which houses these datasets, for providing access to these datasets.

Role of funding agency

Kamala Adhikari was awarded the Vanier Canada Graduate Scholarship (Award code: 201611CGV-382013-267341) by the Canadian Institutes of Health Research and the Alberta Innovates Graduate Studentship Award (Award code: 201611CGV-382013-267341) by the

Alberta Innovates to conduct this study. The funding agencies have no role in study design, data access, analysis, and interpretation, manuscript writing, and in the decision to submit the article for publication.

Data sharing

Additional data such as statistical codes, supplementary tables, and technical appendix are available upon request (by emailing Kamala Adhikari: kamala.adhikaridahal@ucalgary.ca)

Ethical statements

Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary (REB16-2548_REN1). This study used secondary data and all the data were anonymized; therefore, did not require informed consent.

Competing interests

The authors declare that they have no competing interests.

References

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.

2. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151-61.

3. Johnston KM, Gooch K, Korol E, Vo P, Eyawo O, Bradt P, et al. The economic burden of prematurity in Canada. BMC Pediatr. 2014;14:93.

4. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10 Suppl 1:S2.

5. Ward RM, Beachy JC. Neonatal complications following preterm birth. Bjog. 2003;110 Suppl 20:8-16.

6. Canadian Institute for Health Information (CIHI). CIHI Snapshot: Inpatient Hospitalizations, Surgeries, Newborns and Childbirth Indicators. Acesssed from: www.cihi.ca/free_products/cad_hospitalization_and_childbirth_snapshot_2015-2016_en.pdf.

7. Ding XX, Wu YL, Xu SJ, Zhu RP, Jia XM, Zhang SF, et al. Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. J Affect Disord. 2014;159:103-10.

8. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry. 2010;67(10):1012-24.

9. Staneva A, Bogossian F, Pritchard M, Wittkowski A. The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: A systematic review. Women Birth. 2015;28(3):179-93.

10. Rose MS, Pana G, Premji S. Prenatal Maternal Anxiety as a Risk Factor for Preterm Birth and the Effects of Heterogeneity on This Relationship: A Systematic Review and Meta-Analysis. Biomed Res Int. 2016;2016:8312158.

11. Alder J, Fink N, Bitzer J, Hosli I, Holzgreve W. Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? A critical review of the literature. J Matern Fetal Neonatal Med. 2007;20(3):189-209.

12. Misri S, Swift E. Generalized Anxiety Disorder and Major Depressive Disorder in Pregnant and Postpartum Women: Maternal Quality of Life and Treatment Outcomes. J Obstet Gynaecol Can. 2015;37(9):798-803.

13. Wenzel A, Haugen EN, Jackson LC, Brendle JR. Anxiety symptoms and disorders at eight weeks postpartum. J Anxiety Disord. 2005;19(3):295-311.

14. Field T, Diego M, Hernandez-Reif M, Figueiredo B, Deeds O, Ascencio A, et al. Comorbid depression and anxiety effects on pregnancy and neonatal outcome. Infant Behav Dev. 2010;33(1):23-9.

15. Yang S, Kestens Y, Dahhou M, Daniel M, Kramer MS. Neighborhood deprivation and maternal psychological distress during pregnancy: a multilevel analysis. Matern Child Health J. 2015;19(5):1142-51.

16. Kawachi I and Berkman LF. Neighborhood and Health. New York: Oxford University Press Inc.; 2003.

17. Diez Roux AV, Mair C. Neighborhoods and health. Ann N Y Acad Sci. 2010;1186:125-45.

18. Lynch JW, Kaplan GA. Socioeconomic Factors. In: Karachi I and Berkman LF, Social Epidemiology. editor. New York: Oxford University Press; 2000.

19. Dunkel Schetter C. Psychological science on pregnancy: stress processes, biopsychosocial models, and emerging research issues. Annu Rev Psychol. 2011;62:531-58.

20. Kaplan BJ, Giesbrecht GF, Leung BM, Field CJ, Dewey D, Bell RC, et al. The Alberta Pregnancy Outcomes and Nutrition (APrON) cohort study: rationale and methods. Matern Child Nutr. 2014;10(1):44-60.

21. Leung BM, McDonald SW, Kaplan BJ, Giesbrecht GF, Tough SC. Comparison of sample characteristics in two pregnancy cohorts: community-based versus population-based recruitment methods. BMC Med Res Methodol. 2013;13:149.

22. Roberts GBD. Analyses Based on Combining Similar Information from Multiple Surveys. Section on Survey Research Methods Joint Statistical Meetings (JSM); 2009. p. 2138-47.

23. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150:782-6.

24. Rubertsson C, Borjesson K, Berglund A, Josefsson A, Sydsjo G. The Swedish validation of Edinburgh Postnatal Depression Scale (EPDS) during pregnancy. Nord J Psychiatry. 2011;65(6):414-8.

25. Beck CT, Gable RK. Comparative analysis of the performance of the Postpartum Depression Screening Scale with two other depression instruments. Nurs Res. 2001;50(4):242-50.

26. Boyd RC, Le HN, Somberg R. Review of screening instruments for postpartum depression. Arch Womens Ment Health. 2005;8(3):141-53.

27. Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evid Rep Technol Assess (Summ). 2005(119):1-8.

28. Matthey S, Fisher J, Rowe H. Using the Edinburgh postnatal depression scale to screen for anxiety disorders: conceptual and methodological considerations. J Affect Disord. 2013;146(2):224-30.

29. Matthey S. Using the Edinburgh Postnatal Depression Scale to screen for anxiety disorders. Depress Anxiety. 2008;25(11):926-31.

30. Pampalon R, Raymond G. A deprivation index for health and welfare planning in Quebec. Chronic Dis Can. 2000;21(3):104-13.

31. Alberta Health Services. How to use the Pampalon Deprivation Index in Alberta: Research and Innovation, Alberta Health Services; 2016.

32. Canadian Institute for Health Information (CIHI). Reducing gaps in Health: A focus on socioeconomic status in Urban Canada. Ottawa, Ont.: CIHI; 2008.

33. StataCrop. Stata manual release 13. Statistical software. A Stata Press Publication StataCrop LP College Station, Texas, 2013.

34. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj. 2009;338:b2393.

35. Flynn HA, McBride N, Cely A, Wang Y, DeCesare J. Relationship of prenatal depression and comorbidities to infant outcomes. CNS Spectr. 2015;20(1):20-8.

36. Ibanez G, Charles MA, Forhan A, Magnin G, Thiebaugeorges O, Kaminski M, et al. Depression and anxiety in women during pregnancy and neonatal outcome: data from the EDEN mother-child cohort. Early Hum Dev. 2012;88(8):643-9.

37. Pollack MH. Comorbid anxiety and depression. J Clin Psychiatry. 2005;66 Suppl 8:22-9.

38. Kessler RC. Stress, social status, and psychological distress. J Health Soc Behav. 1979;20(3):259-72.

39. Seguin L, Potvin L, St-Denis M, Loiselle J. Chronic stressors, social support, and depression during pregnancy. Obstet Gynecol. 1995;85(4):583-9.

40. McDonald SW, Lyon AW, Benzies KM, McNeil DA, Lye SJ, Dolan SM, et al. The All Our Babies pregnancy cohort: design, methods, and participant characteristics. BMC Pregnancy Childbirth. 2013;13 Suppl 1:S2.

41. Gracie SK, Lyon AW, Kehler HL, Pennell CE, Dolan SM, McNeil DA, et al. All Our Babies Cohort Study: recruitment of a cohort to predict women at risk of preterm birth through the examination of gene expression profiles and the environment. BMC Pregnancy Childbirth. 2010;10:87.

Table 1: Distribution of maternal characteristics across anxiety and depression status during pregnancy

Maternal characteristics	Overall (n=5297)	Absence of both anxiety and depression n=4294 (82.1%)	Presence of anxiety only n=312 (6.0%)	Presence of depression only n=220 (4.2%)	Presence of both anxiety and depression n=402 (7.7%)	$\chi 2$ p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Maternal age						0.006
<35 years	4117 (79.2)	3333 (79.0)	261 (84.5)	156 (72.6)	315 ((81.6)	
≥35 years	1079 (20.8)	886 (21.0)	48 (15.5)	59 (27.4)	71 (18.4)	
Marital status						
Single/divorced/separated	262 (5.1)	168 (3.9)	22 (7.2)	25 (11.5)	47 (11.8)	<0.0001
Married/common-law	4916 (94.9)	4080 (96.1)	284 (92.8)	193 (88.5)	351 (88.2)	
Ethnicity						<0.0001
Non-white	1087 (21.0)	807 (19.0)	68 (22.2)	67 (30.9)	143 (36.1)	
White/Caucasian	4085 (79.0)	3437 (80.9)	239 (77.9)	150 (69.1)	253 (63.9)	
Duration of stay in Canada						<0.0001
Born/5 years+	473 (9.3)	3841 (91.6)	275 (89.9)	185 (87.3)	329 (84.4)	
<5 years	4636 (90.7)	352 (8.4)	31 (10.1)	27 (12.7)	61 (15.6)	
Body mass index						0.002
Underweight (<18.5kg/m^2)	214 (4.3)	170 (4.2)	12 (4.1)	11 (5.3)	21 (5.6)	
Normal weight (18.5 - 24.99 kg/m^2)	3084 (62.5)	2552 (63.2)	172 (58.5)	125 (59.8)	220 (58.4)	
Overweight (25 - 29.99 kg/m^2)	1066 (21.6)	882 (21.9)	59 (20.1)	50 (23.9)	73 (19.4)	
Obesity (≥30 kg/m^2)	574 (11.6)	432 (10.7)	51 (17.4)	23 (11.0)	63 (16.7)	
Parity						<0.0001
Primiparous	2649 (51.3)	2135 (50.3)	199 (64.6)	106 (48.8)	205 (51.9)	
Multiparous	2518 (48.7)	2106 (49.7)	109 (35.4)	111 (51.2)	190 (48.1)	
Unintended pregnancy	1011 (19.5)	742 (17.4)	70 (22.6)	72 (32.9)	122 (30.7)	<0.0001
Smoked before pregnancy	1095 (21.1)	822 (19.3)	86 (27.9)	61 (28.0)	123 (30.9)	<0.0001
Alcohol consumption before pregnancy	4363 (84.1)	3603 (84.7)	268 (87.0)	181 (82.7)	305 (76.6)	<0.0001
Drug abuse before pregnancy	750 (14.5)	561 (13.2)	61 (19.9)	44 (20.4)	83 (20.8)	<0.0001

Maternal characteristics	Overall (n=5297)	Absence of both anxiety and depression n=4294 (82.1%)	Presence of anxiety only n=312 (6.0%)	Presence of depression only n=220 (4.2%)	Presence of both anxiety and depression n=402 (7.7%)	$\chi 2$ p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Maternal education						<0.0001
High school or less than high school	613 (11.9)	451 (10.6)	49 (16.2)	42 (19.4)	68 (17.3)	
Some post-secondary	859 (16.7)	669 (15.8)	57 (18.9)	35 (16.2)	96 (24.4)	
Completed post-secondary	3688 (71.5)	3121 (73.6)	196 (64.9)	139 (64.4)	229 (58.3)	
Household income	477 (9.4)					<0.0001
<$40,000	723 (14.3)	325 (7.8)	25 (8.4)	40 (18.6)	85 (22.0)	
$40,000 - <$70,000	1204 (23.8)	542 (13.0)	53 (17.8)	43 (20.0)	83 (21.5)	
$70,000 - <$100,000	2659 (52.5)	989 (23.8)	76 (25.5)	52 (24.2)	85 (22.0)	
≥$100,000		2301(55.4)	144 (48.3)	80 (37.2)	133 (34.5)	
Inadequate social support anytime during pregnancy	1148 (22.1)	731 (17.1)	77 (25.0)	127 (57.4)	210 (52.4)	<0.0001
Neighborhood deprivation index						<0.0001
Quintile 1 (least deprived)	1323 (27.1)	1108 (27.7)	68 (24.3)	51 (24.9)	80 (22.4)	
Quintile 2	1259 (25.8)	1045 (26.1)	82 (29.3)	41 (20.0)	83 (23.2)	
Quintile 3	972 (19.9)	800 (20.0)	64 (22.9)	39 (19.0)	65 (18.2)	
Quintile 4	736 (15.1)	618 (15.5	37 (13.2)	30 (14.6)	47 (13.1)	
Quintile 5 (most deprived)	595 (12.2)	429 (10.7)	29 (10.4)	44 (21.5)	83 (23.2)	
Preterm birth	356 (7.3)	276 (6.9)	19 (6.5)	16 (8.2)	37 (10.6)	0.068

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

Table 2: Distribution of maternal characteristics across preterm birth status

	Preterm birth n (%)	**Term birth n (%)**	$\chi 2$ **p-value**
Maternal age			0.332
<35yrs	269 (77.1)	3541 (79.3)	
≥35yrs	80 (22.9)	926 (20.7)	
Marital status			0.657
Single/divorced/separated	17 (5.0)	198 (4.4)	
Married/common-law	326 (95.0)	4260 (95.6)	
Ethnicity			0.004
White/Caucasian	253 (73.8)	3574 (80.3)	
Others	90 (26.2)	878 (19.7)	
Duration of stay in Canada			0.061
<5 years	39 (11.6)	380 (8.6)	
Born/5 years+	296 (88.4)	4022 (91.4)	
Body mass index			0.001
Underweight (<18.5kg/m^2)	12 (3.7)	180 (4.2)	
Normal weight (18.5 - 24.99 kg/m^2)	183 (56.3)	2694 (63.3)	
Overweight (25 - 29.99 kg/m^2)	72 (22.2)	924 (21.7)	
Obesity (≥30 kg/m^2)	58 (17.9)	459 (10.8)	
Parity			0.004
Primiparous	201 (58.9)	2266 (50.9)	
Multiparous	140 (41.1)	2184 (49.1)	
Unintended pregnancy	62 (18.0)	829 (18.6)	0.798
Smoked before pregnancy	85 (24.7)	913 (20.5)	0.062
Alcohol consumption before pregnancy	295 (85.8)	3770 (84.5)	0.531
Drug abuse before pregnancy	54 (15.7)	643 (14.4)	0.519
Maternal education			0.891
High school or less than high school	40 (11.7)	487 (11.0)	
Some post-secondary	54 (15.8)	729 (16.4)	
Completed post-secondary	248 (72.5)	3227 (72.6)	
Household income			0.436
<$40,000	34 (10.2)	360 (8.2)	
$40,000 - <$70,000	51 (15.2)	591 (13.5)	
$70,000 - <$100,000	74 (22.1)	1059 (24.2)	
≥$100,000	176 (52.5)	2358 (54.0)	
Inadequate social support anytime during pregnancy	84 (24.2)	955 (21.4)	0.216
Neighborhood deprivation index			0.002
Quintile 1 (least deprived)	93 (26.1)	1176 (27.7)	
Quintile 2	76 (21.4)	1119 (26.3)	
Quintile 3	71 (19.9)	839 (19.8)	
Quintile 4	52 (14.6)	639 (15.0)	
Quintile 5 (most deprived)	64 (18.0)	475 (11.2)	

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

Table 3: 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 neighborhood 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)
Unadjusted:					
Presence of anxiety only	0.9 (0.6, 1.5)	0.8 (0.3, 2.2)	0.8 (0.3, 2.2)	1.1 (0.4, 2.9)	1.3 (0.5, 2.9)
Presence of depression only	1.2 (0.7, 2.1)	0.6 (0.2, 2.1)	0.8 (0.2, 3.6)	1.9 (0.7, 4.2)	2.6 (0.9, 6.1)
Presence of both anxiety and depression	1.6 (1.1, 2.3)	0.2 (0.1, 1.5)	1.3 (0.5, 3.1)	2.8 (1.3, 5.5)	2.5 (1.3, 3.7)
Adjusted for parity, ethnicity, and body mass index:					
Presence of anxiety only	0.8 (0.5, 1.4)	0.7 (0.2, 1.9)	0.7 (0.2, 2.1)	1.0 (0.4, 2.9)	1.0 (0.4, 2.6)
Presence of depression only	1.3 (0.8, 2.3)	0.7 (0.2, 2.4)	0.9 (0.2, 4.1)	1.7 (0.8, 4.7)	2.3 (0.9, 7.0)
Presence of both anxiety and depression	1.6 (1.1, 2.3)	0.2 (0.1, 1.5)	1.4 (0.6, 3.3)	2.6 (1.2, 5.8)	2.2 (1.3, 3.9)

[a]Estimates were from analyses based on multiple imputation; [b]Absence of both anxiety and depression as a reference group; [c]quintile 1: least deprived neighborhood; [d]quintile 5: most deprived neighborhood (quintile 4 and 5 were combined due to few or no cases in some strata); OR: odds ratio; CI: confidence interval

Table 4: Predicted marginal prevalence of preterm birth[a]

Anxiety and depression status during pregnancy[b]	Overall % (95%CI)	Stratified by neighborhood 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	7.1 (6.8, 13.1)	7.6 (5.6, 9.3)	6.4 (4.8, 7.9)	6.9 (5.1, 8.8)	7.6 (5.9, 9.3)
Presence of anxiety only	6.3 (3.3, 9.1)	5.4 (0.2, 10.7)	4.9 (0.3, 9.5)	6.5 (0.3, 12.7)	7.9 (1.3, 14.6)
Presence of depression only	9.6 (5.2, 14.1)	4.7 (0.5, 10.4)	5.7 (0.45, 13.4)	13.3 (3.4, 23.2)	14.0 (2.7, 25.3)
Presence of both anxiety and depression	10.0 (6.8, 13.1)	1.4 (0.1, 4.2)	8.0 (1.9, 14.1)	15.9 (6.3, 25.6)	15.7 (9.5, 22.6)

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

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4, and 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6 and 7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7 and 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7 and 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9, 10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9, 10
Bias	9	Describe any efforts to address potential sources of bias	8, 9, 10
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9, 10
		(*b*) Describe any methods used to examine subgroups and interactions	9, 10
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	12

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Not provided now: can be provided if requested
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, 11, 12, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	10, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11, Table 2 and 3
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not done
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11 and Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13, 14, 15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17, 18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Neighborhood socioeconomic status modifies the association between anxiety and depression during pregnancy and preterm birth: A Community-based Canadian Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031035.R2
Article Type:	Original research
Date Submitted by the Author:	28-Dec-2019
Complete List of Authors:	Adhikari, Kamala; University of Calgary Cumming School of Medicine Patten, Scott Williamson, Tyler; University of Calgary Cumming School of Medicine, Community Health Sciences Patel, Alka Premji, Shahirose ; York University, Tough, Suzanne ; University of Calgary Cumming School of Medicine, Paediatrics and Community Health Science Letourneau, Nicole Giesbrecht, Gerald Metcalfe, Amy; University of Calgary, Obstetrics and Gynecology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Obstetrics and gynaecology, Public health
Keywords:	MENTAL HEALTH, EPIDEMIOLOGY, Preterm birth, Neighbourhood socioeconomic status

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Neighborhood socioeconomic status modifies the association between anxiety and depression during pregnancy and preterm birth: A Community-based Canadian Cohort Study

Kamala Adhikari[1], Scott B Patten[1], Tyler Williamson[1], Alka B Patel[1,2], Shahirose Premji[3], Suzanne Tough[1,4], Nicole Letourneau[1,4,5,8], Gerald Giesbrecht[1,4], Amy Metcalfe[1,6,7]

[1]Department of Community Health Sciences, University of Calgary, Calgary, Canada; [2]Applied Research and Evaluation- Primary Health Care, Alberta Health Services, Calgary, Canada; [3]School of Nursing, Faculty of Health, York University, Calgary, Canada; [4]Department of Pediatrics, University of Calgary, Calgary, Canada; [5]Faculty of Nursing University of Calgary, Calgary, Canada; [6]Department of Obstetrics and Gynecology, University of Calgary, Calgary, Canada; [7]Department of Medicine, University of Calgary, Calgary, Canada; [8]Deprtment of Psychiatry, University of Calgary, Calgary, Canada

Corresponding author:

Kamala Adhikari

Department of Community Health Sciences, University of Calgary

3280 Hospital Drive NW, Calgary, AB, T2N 4Z6

Email: kamala.adhikaridahal@ucalgary.ca

Telephone number: 1+5870-700-7531

ORCID number: 0000-0003-2872-9496

Word Count: 3686

Abstract

Objective: This study examined the association of anxiety alone, depression alone, and the presence of both anxiety and depression with PTB and further examined whether neighborhood socioeconomic status (SES) modified this association.

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 neighborhood SES data from the 2011 Canadian census.

Setting: Calgary, Alberta, Canada

Participants: Overall, 5,538 pregnant women who were <27 weeks of gestation and >15 years old were enrolled in the cohort studies between 2008 and 2012. 3,341 women participated in the AOF study and 2,187 women participated in the APrON study, with 231 women participated in both studies. Women who participated in both studies were only counted once.

Primary and secondary outcome measures: PTB was defined as delivery prior to 37 weeks of gestation. 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.

Results: Overall, 7.3% of women delivered preterm infants. The presence of both anxiety and depression, but neither of these conditions alone, was significantly associated with PTB

(OR=1.6, 95% CI=1.1, 2.3) and had significant interaction with neighborhood deprivation (p-value=0.004). The predicted probability of PTB for women with both anxiety and depression was 10.0%, which increased to 15.7% if they lived in the most deprived neighborhoods and decreased to 1.4% if they lived in the least deprived neighborhoods.

Conclusions: Effects of anxiety and depression on 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 and depression, neighborhood socioeconomic status, deprivation, preterm birth

Article summary: strengths and limitations of this study

- This study used data from two community-based prospective pregnancy cohort studies that were conducted in a relatively representative sample (compared to a hospital-based or clinic-based sample) of pregnant women.
- This study performed statistical analysis to examine the relationship between anxiety and depression during pregnancy and preterm birth by analyzing the presence of both depressive and anxious symptoms versus isolated depressive or anxious symptoms as risk factors of preterm birth, and further analyzing whether neighborhood socioeconomic status modifies the relationship.
- This study analyzed overall preterm birth as data on spontaneous and iatrogenic preterm birth were not available.
- The study sample over-represents women from urban areas of Alberta, with high socioeconomic status, thus limiting the generalizability of the findings to urban settings.
- The use of self-reported anxiety and depression measurement scales may introduce measurement inaccuracy.

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%.(1) Preterm birth (PTB) is responsible for 35% of neonatal deaths globally.(2) 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.(3-5) Despite substantial research and interventions to prevent PTB, the incidence of PTB has not declined and its etiology remains unclear.(1, 6) Understanding the risk factors for PTB, such as psychosocial distress and neighborhood low 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.(7-10) 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.(7, 9, 10) Notably, most of the previous studies analyzed anxiety or depression without considering that they may occur in a comorbid state.(7-11) 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.(12-14) 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 neighborhood SES.(15) Neighborhood SES is an area-level measure of SES, which aggregates individual SES (such as

income, education, and employment status) at a certain geographical level.(16) Neighborhood SES may influence the risk of PTB by exposing women to health benefitting or risk elevating factors, such as access to healthy foods, quality health services, opportunities for leisure activity, and social support and exposure to societal stressors, crimes, and poor air and water quality.(16-19) Low neighborhood SES may affect an individual's ability to fulfill daily needs, access resources, make lifestyle choices, and cope with different situations.(16-19) Thus, the risk of PTB that is associated with anxiety and/or depression during pregnancy may differ by neighborhood 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 neighborhood 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. Women contributed only one pregnancy in the cohort. Women who participated in both studies were only counted once. The description and comparability of these two cohort studies is available elsewhere,(20, 21) and justifies combining these data sources.(22) The AOF study aimed to

examine maternal well-being and infant outcomes and the APrON study aimed to investigate the role of prenatal maternal nutrition on maternal mental health and infant outcomes.(20, 21) Briefly, each cohort study had similar inclusion criteria, sampling design (community-based, non-stratified sampling), and data collection methods.(21) Both studies recruited pregnancy cohorts between 2008 and 2012 using community-based recruitment strategies (such as face-to-face recruitment in maternity clinics by research assistants or nurses and recruitment in public places using posters, pamphlets, and brochures) and followed them up. The follow-up for mother and child dyad is still ongoing in both studies.(21)

We obtained two de-identified cohort datasets linked with neighborhood 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.

Patient and public involvement

This study used de-identified secondary data. Patient and public were not involved in the design or planning of the study.

Variables

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. Data on age, ethnicity (white includes all Caucasians and non-white includes all non-Caucasians), maternal SES, parity, body mass index (BMI), smoking status, social support, depression, and anxiety were collected at <27 weeks of gestation (in the APrON study) and at <25 weeks of gestation (in the AOF study). BMI was calculated based on the self-reported pre-pregnancy height and weight (i.e., immediately before pregnancy). Additionally, depression and

anxiety were measured during the third trimester (APrON: 27-42 weeks of gestation; AOF: 34-36 weeks of gestation).(20, 21)

Both cohorts used an identical measure of depression, i.e., the Edinburgh 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).(23) The EPDS has high internal consistency of 0.87,(23) a sensitivity of 78%, and specificity of 99% in the obstetric population,(24, 25) and is the most common scale used to measure antenatal and postnatal depression.(26) 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.(27) 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 by previous studies,(28, 29) with a sensitivity of 66.7% and specificity of 88.2% in the obstetric population.(29)The standard cut-off of ≥6 out of a maximum of 9 is used to define the presence of clinically significant anxiety during pregnancy.(29) 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 EDPS-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 isolated anxiety or depression was defined as meeting the anxiety or depression definition during pregnancy. Presence of both anxiety and depression was defined as meeting both anxiety and depression definitions at the same time point in pregnancy. Births that occurred before 37 weeks of gestation were defined as PTB (both spontaneous and iatrogenic included). PTB was measured at 4 months of postpartum period based on maternal recall of week of gestation at delivery.

Neighborhood SES data were measured by the Pampalon material deprivation index (derived from the 2011 Statistics Canada census)(30, 31) which was aggregated at the dissemination area (DA) level. DA is the smallest geographical unit available in the Canadian census, consisting of 400-700 persons.(32) The Pampalon material deprivation index is a composite measure of neighborhood 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 deprivation quintile, with quintile 1 representing the least deprived and quintile 5 representing the most deprived neighborhoods.(30) Neighborhood SES was assigned to each cohort based on their postal code of residence at the time of cohort recruitment.

Data Analysis

Bivariate analysis was used to identify variables associated with PTB as well as anxiety and/or depression ("anxiety only," "depression only," and "both anxiety and depression"). The significantly associated ($p<0.05$) variables were parity, ethnicity, and body mass index. A multivariable logistic regression model was constructed to examine the association between anxiety and/or depression and PTB. The model also included parity, ethnicity, BMI, maternal age, smoking, social support, maternal education, and household total income variables. These variables were selected to adjust for in the model based on our prior knowledge (or conceptual understanding based on literature) that they are associated with both outcome (i.e., PTB) and exposure (i.e., anxiety and/or depression) but do not reside in the causal pathway of the relationship between anxiety and/or depression and PTB. The underlying hypothetical relationship of the variables have been shown using a direct acyclic diagram (supplementary file: Figure 1)

A multilevel multivariable logistic regression model, which assumes the lack of

independence of observations and accounts for the variation between groups or areas, was then constructed to examine the effect modification of neighborhood SES on the association between anxiety and/or depression and PTB. This model included interaction terms in addition to parity, ethnicity, BMI, maternal age, smoking, social support, maternal education, and household total income variables. The interaction terms comprised "anxiety only," "depression only," and "both anxiety and depression" combined with each quintile of deprivation indices. Deprivation quintile 4th and 5th 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. 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, BMI, maternal age, smoking, social support, maternal education, and household total income variables, across observations) was estimated using the model with interaction terms. Alpha (α) of <0.05 was used to determine statistical significance. All analyses were performed using STATA/IC 14.1.

Missing Data

The proportion of missing data for gestational age at delivery (PTB) was 7.5%, for neighborhood deprivation indices was 7.8%, and for body mass index was 6.8%. Other variables had missing data <5%, ranging from 1.3% for depression to 4.4% for household total income. The missing data for these variables occurred due to maternal non-response. Characteristics of groups of women (such as ethnicity, parity, BMI, neighborhood SES, anxiety and depression) with and without missing data on PTB were compared to assess differences. Multiple imputation

was used to address with missing data on the three variables (i.e., PTB , body mass index, and neighborhood deprivation indices) that had ≥5% missing data .(33) Using STATA's "mi Package", the multiple imputation process was carried out in three steps as recommended by Rubin: imputation, analysis, and combination.(33, 34) The method assumes that the missing data are missing at random and attempts to estimate a missing value within a plausible set of values.(33, 34) The imputation values (i.e., a predictive distribution based on observed data) were estimated using an imputation model (with imputation 50 times).(33, 34) The imputation model included the variables that were significant with missing data (i.e., marital status, duration of stay in Canada, intended pregnancy, alcohol consumption) as well as those that were utilized in the analysis model (i.e., PTB, ethnicity, parity, BMI, maternal age, smoking, social support maternal education, household total income, neighborhood SES, anxiety and depression, and interaction terms). Sensitivity analysis was done to compare the estimates from the analyses based on multiple imputation and from the analysis restricted to complete case.

RESULTS

Of total 5,297 pregnant women, 17.9% of women had anxiety and/or depression: 7.7% of women had both anxiety and depression, followed by 6.0% women had anxiety alone, and 4.2% women had depression alone. Women with both anxiety and depression had a higher rate of PTB (10.6%) compared to those with isolated anxiety (6.5%) or isolated depression (8.2%) or without anxiety and depression (6.9%). A higher proportion of women with a presence of 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 neighborhoods ($p<0.05$) (Table 1). Mean scores of anxiety (mean=6.6, standard deviation

(SD)=0.4) and depression (mean=16.2, SD=0.1) were higher among women with both conditions compared to those with anxiety alone (mean=6.1, SD=0.2) or depression alone (mean=14.6, SD=0.1). As shown in Table 2, women who delivered preterm infants were more likely to be non-white, obese, primiparous, and from the most deprived neighborhoods. Variables such as maternal ethnicity, parity, BMI, neighborhood SES, anxiety, and depression were significantly associated with the presence of missing data on PTB.

The presence of both anxiety and depression (adjusted odds ratio (aOR)=1.6, 95% CI=1.1, 2.3), but neither anxiety alone (aOR=0.8, 95% CI=0.6, 1.6) nor depression alone (aOR=1.3, 95% CI=0.8, 2.5), was significantly associated with PTB (Table 3). Effect modification was observed between the presence of both anxiety and depression and neighborhood SES (p-value=0.004). Compared to women without anxiety and depression, women with both anxiety and depression who lived in quintile 3 and more deprived neighborhoods had significantly increased odds of experiencing a preterm delivery (quintile 4 and 5: aOR=2.2, 95% CI=1.3, 4.0). In contrast, compared to women without anxiety and depression, women with both anxiety and depression who lived in the least deprived neighborhood were not at elevated odds of experiencing a preterm delivery (aOR=0.2, 95 % CI=0.1, 1.5) (Table 3). The OR estimates from the analyses based on multiple imputation and from the analysis restricted to complete cases were similar, with some confidence intervals being slightly narrower in the multiple imputation analysis.

As shown in Table 4, the predicted probability of PTB for women with a presence of both anxiety and depression was 10.0% (95% CI=6.8, 13.1). It increased to 15.7% (95% CI=9.5, 23.2) if they lived in the most deprived neighborhoods – an increase of 57.1% – and it decreased to 1.4% (95% CI=0.1, 4.2) if they lived in the least deprived neighborhoods. The predicted

probability of PTB for women with depression alone was 9.6% (95% CI=5.2, 14.1), which increased to 14.1% (95% CI=2.7, 25.3) if they lived in the most deprived neighborhoods. The predicted probability for women with anxiety alone and women with absence of anxiety and depression remained similar across the neighborhood deprivation indices.

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 neighborhood SES. Women with both anxiety and depression were more likely to deliver preterm infants if they lived in a relatively more deprived neighborhood compared to if they lived in a less deprived neighborhood. 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 neighborhood and it was 1% if they lived in the least deprived neighborhood. Overall, the findings suggest the importance of neighborhoods on maternal health (in general) and more specifically preterm birth.

Interpretation

Although few previous studies assessed the association between the presence of both anxiety and depression during pregnancy and PTB, our finding is consistent with their findings that the presence of both anxiety and depression increases the likelihood of PTB.(14, 35, 36) This may be related to the additive effects of prenatal depression and anxiety and the effects of

severity of anxiety and depressive symptoms. 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.(36, 37). 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.(12, 35, 37) Thus, the presence of both anxiety and depression during pregnancy may lead to an increased risk of poor birth outcomes, including PTB, relative to depression or anxiety alone.

Our study did not find an association between anxiety alone or depression alone and PTB, which is consistent with a previous pregnancy cohort study that analyzed isolated anxiety or depression separately from the presence of both or comorbid anxiety and depression.(36) However, the finding is inconsistent with several previous studies that analyzed anxiety or depression intermixing with the presence of both conditions.(8, 10) 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 neighborhood SES, meaning that these studies averaged the

association across neighborhood 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 neighborhood may reflect that, besides individual level risk factors, PTB is related to neighborhood factors.(16-18) For example, women living in deprived neighborhoods often have less access to healthy foods, quality health services, and opportunities for leisure activity, and have more exposure to societal stressors and crimes.(16-19) 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.(8, 11, 38, 39) 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 neighborhoods 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 neighborhood 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 neighborhood 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 neighborhood 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 infants, 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,(21, 40, 41) 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 may have introduced measurement inaccuracy. Specifically, the EPDS-3A scale has not been validated in a pregnant population and it tends to provide high false-positive results based on its validation on during the postpartum period.(28, 29) 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 since they were not available in the study's data

sources. Similarly, we were not able to separate out spontaneous and iatrogenic PTB in the model – the association might be stronger for spontaneous PTB. Overall, replication of this study addressing these limitations may further the understanding on risk factors and preventive strategies of PTB.

We defined neighborhoods using the smallest area (i.e., dissemination area) where people living in the smallest area are more likely to be similar for the outcomes, used multilevel analysis that accounts for area-level variation, and adjusted for individual level variables, an appropriate analytical approach for multilevel data. However, it is difficult to interpret the influence of neighborhood SES using area-based variables, where women living in the same area share the same value for the variable. 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.

Conclusions

Our study found that the presence of both prenatal anxiety and depression increases the likelihood of PTB and the effect of this combination is stronger for women living in low SES neighborhoods compared to women living in high SES neighborhoods. The finding may help to inform development of intervention strategies (such as timely screening and management of anxiety and depression) that focus on the most deprived neighborhood. 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.

Authors contributions

Kamala Adhikari involved in the conception and design of the study. Kamala is also responsible for conducting the analysis, interpreting the data, and drafting the manuscript. 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 manuscript. Scott Patten, Tyler Williamson, Alka B Patel, Shahirose Premji, Suzanne Tough, Nicole Letourneau, and Gerald Giesbrecht were involved in the conception and design of the study and provided interpretation and intellectual content to subsequent drafts of the manuscript. All authors read and approved the final draft.

Acknowledgements

Kamala Adhikari was awarded the Vanier Canada Graduate Scholarship and the Alberta Innovates Graduate Studentship Award. Amy Metcalfe is supported by a Canadian Institutes of Health Research New Investigator Award. We acknowledge the All Our Families and the Alberta Pregnancy Outcomes and Nutrition cohort study teams for providing permission to use their data. We acknowledge SAGE (Secondary Analysis to Generate Evidence), the secure data repository developed by PolicyWise for Children and Families, which houses these datasets, for providing access to these datasets.

Role of funding agency

Kamala Adhikari was awarded the Vanier Canada Graduate Scholarship (Award code: 201611CGV-382013-267341) by the Canadian Institutes of Health Research and the Alberta Innovates Graduate Studentship Award (Award code: 201611CGV-382013-267341) by the

Alberta Innovates to conduct this study. The funding agencies have no role in study design, data access, analysis, and interpretation, manuscript writing, and in the decision to submit the article for publication.

Data sharing

Additional data such as statistical codes, supplementary tables, and technical appendix are available upon request (by emailing Kamala Adhikari: kamala.adhikaridahal@ucalgary.ca)

Ethical statements

Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary (REB16-2548_REN1). This study used secondary data and all the data were anonymized; therefore, did not require informed consent.

Competing interests

The authors declare that they have no competing interests.

References

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.

2. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151-61.

3. Johnston KM, Gooch K, Korol E, Vo P, Eyawo O, Bradt P, et al. The economic burden of prematurity in Canada. BMC Pediatr. 2014;14:93.

4. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10 Suppl 1:S2.

5. Ward RM, Beachy JC. Neonatal complications following preterm birth. Bjog. 2003;110 Suppl 20:8-16.

6. Canadian Institute for Health Information (CIHI). CIHI Snapshot: Inpatient Hospitalizations, Surgeries, Newborns and Childbirth Indicators. Acesssed from: www.cihi.ca/free_products/cad_hospitalization_and_childbirth_snapshot_2015-2016_en.pdf.

7. Ding XX, Wu YL, Xu SJ, Zhu RP, Jia XM, Zhang SF, et al. Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. J Affect Disord. 2014;159:103-10.

8. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry. 2010;67(10):1012-24.

9. Staneva A, Bogossian F, Pritchard M, Wittkowski A. The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: A systematic review. Women Birth. 2015;28(3):179-93.

10. Rose MS, Pana G, Premji S. Prenatal Maternal Anxiety as a Risk Factor for Preterm Birth and the Effects of Heterogeneity on This Relationship: A Systematic Review and Meta-Analysis. Biomed Res Int. 2016;2016:8312158.

11. Alder J, Fink N, Bitzer J, Hosli I, Holzgreve W. Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? A critical review of the literature. J Matern Fetal Neonatal Med. 2007;20(3):189-209.

12. Misri S, Swift E. Generalized Anxiety Disorder and Major Depressive Disorder in Pregnant and Postpartum Women: Maternal Quality of Life and Treatment Outcomes. J Obstet Gynaecol Can. 2015;37(9):798-803.

13. Wenzel A, Haugen EN, Jackson LC, Brendle JR. Anxiety symptoms and disorders at eight weeks postpartum. J Anxiety Disord. 2005;19(3):295-311.

14. Field T, Diego M, Hernandez-Reif M, Figueiredo B, Deeds O, Ascencio A, et al. Comorbid depression and anxiety effects on pregnancy and neonatal outcome. Infant Behav Dev. 2010;33(1):23-9.

15. Yang S, Kestens Y, Dahhou M, Daniel M, Kramer MS. Neighborhood deprivation and maternal psychological distress during pregnancy: a multilevel analysis. Matern Child Health J. 2015;19(5):1142-51.

16. Kawachi I and Berkman LF. Neighborhood and Health. New York: Oxford University Press Inc.; 2003.

17. Diez Roux AV, Mair C. Neighborhoods and health. Ann N Y Acad Sci. 2010;1186:125-45.

18. Lynch JW, Kaplan GA. Socioeconomic Factors. In: Karachi I and Berkman LF, Social Epidemiology. editor. New York: Oxford University Press; 2000.

19. Dunkel Schetter C. Psychological science on pregnancy: stress processes, biopsychosocial models, and emerging research issues. Annu Rev Psychol. 2011;62:531-58.

20. Kaplan BJ, Giesbrecht GF, Leung BM, Field CJ, Dewey D, Bell RC, et al. The Alberta Pregnancy Outcomes and Nutrition (APrON) cohort study: rationale and methods. Matern Child Nutr. 2014;10(1):44-60.

21. Leung BM, McDonald SW, Kaplan BJ, Giesbrecht GF, Tough SC. Comparison of sample characteristics in two pregnancy cohorts: community-based versus population-based recruitment methods. BMC Med Res Methodol. 2013;13:149.

22. Roberts GBD. Analyses Based on Combining Similar Information from Multiple Surveys. Section on Survey Research Methods Joint Statistical Meetings (JSM); 2009. p. 2138-47.

23. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150:782-6.

24. Rubertsson C, Borjesson K, Berglund A, Josefsson A, Sydsjo G. The Swedish validation of Edinburgh Postnatal Depression Scale (EPDS) during pregnancy. Nord J Psychiatry. 2011;65(6):414-8.

25. Beck CT, Gable RK. Comparative analysis of the performance of the Postpartum Depression Screening Scale with two other depression instruments. Nurs Res. 2001;50(4):242-50.

26. Boyd RC, Le HN, Somberg R. Review of screening instruments for postpartum depression. Arch Womens Ment Health. 2005;8(3):141-53.

27. Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evid Rep Technol Assess (Summ). 2005(119):1-8.

28. Matthey S, Fisher J, Rowe H. Using the Edinburgh postnatal depression scale to screen for anxiety disorders: conceptual and methodological considerations. J Affect Disord. 2013;146(2):224-30.

29. Matthey S. Using the Edinburgh Postnatal Depression Scale to screen for anxiety disorders. Depress Anxiety. 2008;25(11):926-31.

30. Pampalon R, Raymond G. A deprivation index for health and welfare planning in Quebec. Chronic Dis Can. 2000;21(3):104-13.

31. Alberta Health Services. How to use the Pampalon Deprivation Index in Alberta: Research and Innovation, Alberta Health Services; 2016.

32. Canadian Institute for Health Information (CIHI). Reducing gaps in Health: A focus on socioeconomic status in Urban Canada. Ottawa, Ont.: CIHI; 2008.

33. StataCrop. Stata manual release 13. Statistical software. A Stata Press Publication StataCrop LP College Station, Texas, 2013.

34. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj. 2009;338:b2393.

35. Flynn HA, McBride N, Cely A, Wang Y, DeCesare J. Relationship of prenatal depression and comorbidities to infant outcomes. CNS Spectr. 2015;20(1):20-8.

36. Ibanez G, Charles MA, Forhan A, Magnin G, Thiebaugeorges O, Kaminski M, et al. Depression and anxiety in women during pregnancy and neonatal outcome: data from the EDEN mother-child cohort. Early Hum Dev. 2012;88(8):643-9.

37. Pollack MH. Comorbid anxiety and depression. J Clin Psychiatry. 2005;66 Suppl 8:22-9.

38. Kessler RC. Stress, social status, and psychological distress. J Health Soc Behav. 1979;20(3):259-72.

39. Seguin L, Potvin L, St-Denis M, Loiselle J. Chronic stressors, social support, and depression during pregnancy. Obstet Gynecol. 1995;85(4):583-9.

40. McDonald SW, Lyon AW, Benzies KM, McNeil DA, Lye SJ, Dolan SM, et al. The All Our Babies pregnancy cohort: design, methods, and participant characteristics. BMC Pregnancy Childbirth. 2013;13 Suppl 1:S2.

41. Gracie SK, Lyon AW, Kehler HL, Pennell CE, Dolan SM, McNeil DA, et al. All Our Babies Cohort Study: recruitment of a cohort to predict women at risk of preterm birth through the examination of gene expression profiles and the environment. BMC Pregnancy Childbirth. 2010;10:87.

Table 1: Distribution of maternal characteristics across anxiety and depression status during pregnancy

Maternal characteristics	Overall (n=5297)	Absence of both anxiety and depression n=4294 (82.1%)	Presence of anxiety only n=312 (6.0%)	Presence of depression only n=220 (4.2%)	Presence of both anxiety and depression n=402 (7.7%)	$\chi 2$ p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Maternal age						0.006
<35 years	4117 (79.2)	3333 (79.0)	261 (84.5)	156 (72.6)	315 ((81.6)	
≥35 years	1079 (20.8)	886 (21.0)	48 (15.5)	59 (27.4)	71 (18.4)	
Marital status						
Single/divorced/separated	262 (5.1)	168 (3.9)	22 (7.2)	25 (11.5)	47 (11.8)	<0.0001
Married/common-law	4916 (94.9)	4080 (96.1)	284 (92.8)	193 (88.5)	351 (88.2)	
Ethnicity						<0.0001
Non-white	1087 (21.0)	807 (19.0)	68 (22.2)	67 (30.9)	143 (36.1)	
White/Caucasian	4085 (79.0)	3437 (80.9)	239 (77.9)	150 (69.1)	253 (63.9)	
Duration of stay in Canada						<0.0001
Born/5 years+	473 (9.3)	3841 (91.6)	275 (89.9)	185 (87.3)	329 (84.4)	
<5 years	4636 (90.7)	352 (8.4)	31 (10.1)	27 (12.7)	61 (15.6)	
Body mass index						0.002
Underweight (<18.5kg/m^2)	214 (4.3)	170 (4.2)	12 (4.1)	11 (5.3)	21 (5.6)	
Normal weight (18.5 - 24.99 kg/m^2)	3084 (62.5)	2552 (63.2)	172 (58.5)	125 (59.8)	220 (58.4)	
Overweight (25 - 29.99 kg/m^2)	1066 (21.6)	882 (21.9)	59 (20.1)	50 (23.9)	73 (19.4)	
Obesity (≥30 kg/m^2)	574 (11.6)	432 (10.7)	51 (17.4)	23 (11.0)	63 (16.7)	
Parity						<0.0001
Primiparous	2649 (51.3)	2135 (50.3)	199 (64.6)	106 (48.8)	205 (51.9)	
Multiparous	2518 (48.7)	2106 (49.7)	109 (35.4)	111 (51.2)	190 (48.1)	
Unintended pregnancy	1011 (19.5)	742 (17.4)	70 (22.6)	72 (32.9)	122 (30.7)	<0.0001
Smoked before pregnancy	1095 (21.1)	822 (19.3)	86 (27.9)	61 (28.0)	123 (30.9)	<0.0001
Alcohol consumption before pregnancy	4363 (84.1)	3603 (84.7)	268 (87.0)	181 (82.7)	305 (76.6)	<0.0001
Drug abuse before pregnancy	750 (14.5)	561 (13.2)	61 (19.9)	44 (20.4)	83 (20.8)	<0.0001

Maternal characteristics	Overall (n=5297)	Absence of both anxiety and depression n=4294 (82.1%)	Presence of anxiety only n=312 (6.0%)	Presence of depression only n=220 (4.2%)	Presence of both anxiety and depression n=402 (7.7%)	$\chi 2$ p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Maternal education						<0.0001
High school or less than high school	613 (11.9)	451 (10.6)	49 (16.2)	42 (19.4)	68 (17.3)	
Some post-secondary	859 (16.7)	669 (15.8)	57 (18.9)	35 (16.2)	96 (24.4)	
Completed post-secondary	3688 (71.5)	3121 (73.6)	196 (64.9)	139 (64.4)	229 (58.3)	
Household income	477 (9.4)					<0.0001
<$40,000	723 (14.3)	325 (7.8)	25 (8.4)	40 (18.6)	85 (22.0)	
$40,000 - <$70,000	1204 (23.8)	542 (13.0)	53 (17.8)	43 (20.0)	83 (21.5)	
$70,000 - <$100,000	2659 (52.5)	989 (23.8)	76 (25.5)	52 (24.2)	85 (22.0)	
≥$100,000		2301(55.4)	144 (48.3)	80 (37.2)	133 (34.5)	
Inadequate social support anytime during pregnancy	1148 (22.1)	731 (17.1)	77 (25.0)	127 (57.4)	210 (52.4)	<0.0001
Neighborhood deprivation index						<0.0001
Quintile 1 (least deprived)	1323 (27.1)	1108 (27.7)	68 (24.3)	51 (24.9)	80 (22.4)	
Quintile 2	1259 (25.8)	1045 (26.1)	82 (29.3)	41 (20.0)	83 (23.2)	
Quintile 3	972 (19.9)	800 (20.0)	64 (22.9)	39 (19.0)	65 (18.2)	
Quintile 4	736 (15.1)	618 (15.5	37 (13.2)	30 (14.6)	47 (13.1)	
Quintile 5 (most deprived)	595 (12.2)	429 (10.7)	29 (10.4)	44 (21.5)	83 (23.2)	
Preterm birth	356 (7.3)	276 (6.9)	19 (6.5)	16 (8.2)	37 (10.6)	0.068

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

Table 2: Distribution of maternal characteristics across preterm birth status

	Preterm birth n (%)	**Term birth n (%)**	$\chi 2$ **p-value**
Maternal age			0.332
<35yrs	269 (77.1)	3541 (79.3)	
≥35yrs	80 (22.9)	926 (20.7)	
Marital status			0.657
Single/divorced/separated	17 (5.0)	198 (4.4)	
Married/common-law	326 (95.0)	4260 (95.6)	
Ethnicity			0.004
White/Caucasian	253 (73.8)	3574 (80.3)	
Others	90 (26.2)	878 (19.7)	
Duration of stay in Canada			0.061
<5 years	39 (11.6)	380 (8.6)	
Born/5 years+	296 (88.4)	4022 (91.4)	
Body mass index			0.001
Underweight (<18.5kg/m^2)	12 (3.7)	180 (4.2)	
Normal weight (18.5 - 24.99 kg/m^2)	183 (56.3)	2694 (63.3)	
Overweight (25 - 29.99 kg/m^2)	72 (22.2)	924 (21.7)	
Obesity (≥30 kg/m^2)	58 (17.9)	459 (10.8)	
Parity			0.004
Primiparous	201 (58.9)	2266 (50.9)	
Multiparous	140 (41.1)	2184 (49.1)	
Unintended pregnancy	62 (18.0)	829 (18.6)	0.798
Smoked before pregnancy	85 (24.7)	913 (20.5)	0.062
Alcohol consumption before pregnancy	295 (85.8)	3770 (84.5)	0.531
Drug abuse before pregnancy	54 (15.7)	643 (14.4)	0.519
Maternal education			0.891
High school or less than high school	40 (11.7)	487 (11.0)	
Some post-secondary	54 (15.8)	729 (16.4)	
Completed post-secondary	248 (72.5)	3227 (72.6)	
Household income			0.436
<$40,000	34 (10.2)	360 (8.2)	
$40,000 - <$70,000	51 (15.2)	591 (13.5)	
$70,000 - <$100,000	74 (22.1)	1059 (24.2)	
≥$100,000	176 (52.5)	2358 (54.0)	
Inadequate social support anytime during pregnancy	84 (24.2)	955 (21.4)	0.216
Neighborhood deprivation index			0.002
Quintile 1 (least deprived)	93 (26.1)	1176 (27.7)	
Quintile 2	76 (21.4)	1119 (26.3)	
Quintile 3	71 (19.9)	839 (19.8)	
Quintile 4	52 (14.6)	639 (15.0)	
Quintile 5 (most deprived)	64 (18.0)	475 (11.2)	

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

Table 3: 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 neighborhood 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)
Unadjusted:					
Presence of anxiety only	0.9 (0.6, 1.5)	0.8 (0.3, 2.2)	0.8 (0.3, 2.2)	1.1 (0.4, 2.9)	1.3 (0.5, 2.9)
Presence of depression only	1.2 (0.7, 2.1)	0.6 (0.2, 2.1)	0.8 (0.2, 3.6)	1.9 (0.7, 4.2)	2.6 (0.9, 6.1)
Presence of both anxiety and depression	1.6 (1.1, 2.3)	0.2 (0.1, 1.5)	1.3 (0.5, 3.1)	2.8 (1.3, 5.5)	2.5 (1.3, 3.7)
Adjusted for parity, ethnicity, body mass index, maternal age, smoking, social support, maternal education, and household total income:					
Presence of anxiety only	0.8 (0.6, 1.6)	0.7 (0.2, 1.9)	0.7 (0.2, 2.1)	1.0 (0.4, 2.9)	1.0 (0.4, 2.6)
Presence of depression only	1.3 (0.8, 2.5)	0.7 (0.2, 2.5)	0.9 (0.2, 4.1)	1.7 (0.8, 4.7)	2.1 (0.9, 7.0)
Presence of both anxiety and depression	1.6 (1.1, 2.3)	0.2 (0.1, 1.5)	1.4 (0.6, 3.3)	2.1 (1.2, 5.8)	2.2 (1.3, 4.0)

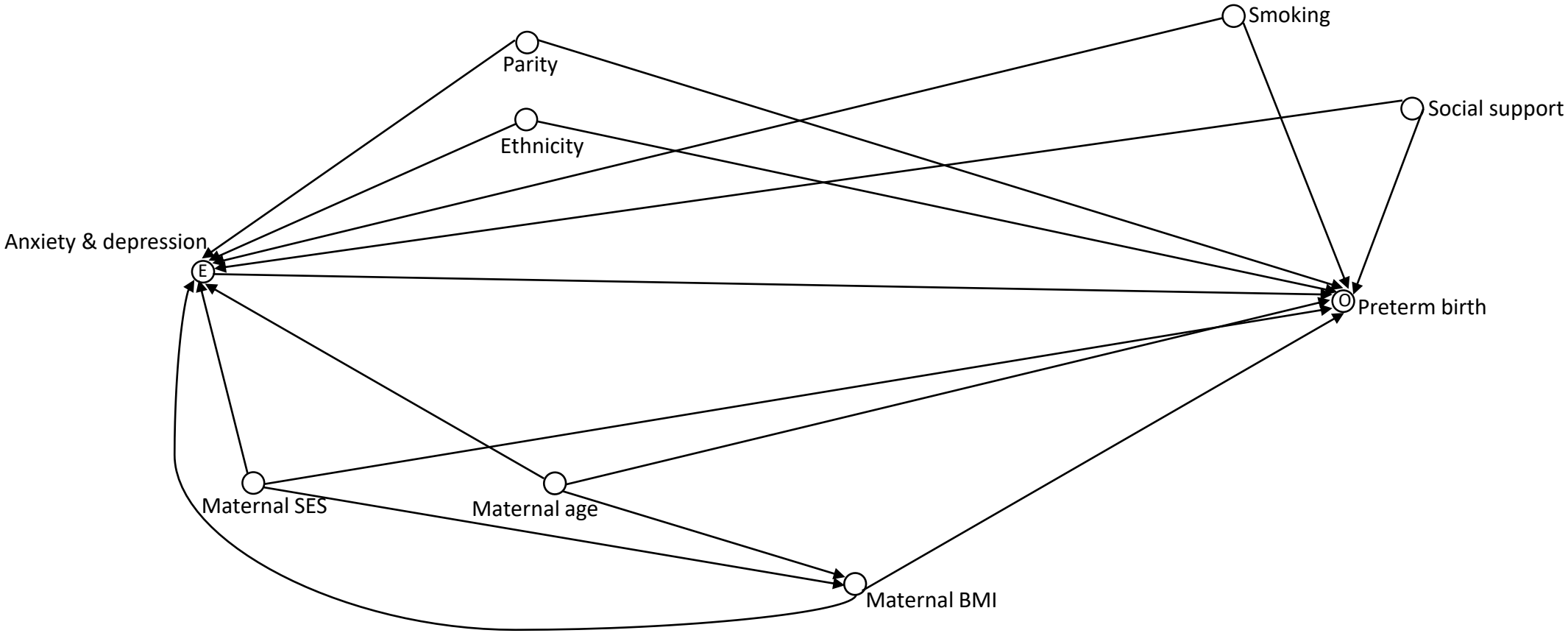
[a]Estimates were from analyses based on multiple imputation; [b]Absence of both anxiety and depression as a reference group; [c]quintile 1: least deprived neighborhood; [d]quintile 5: most deprived neighborhood (quintile 4 and 5 were combined due to few or no cases in some strata); OR: odds ratio; CI: confidence interval

Table 4: Predicted marginal prevalence of preterm birth[a]

Anxiety and depression status during pregnancy[b]	Overall % (95%CI)	Stratified by neighborhood 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	7.1 (6.8, 13.1)	7.6 (5.6, 9.3)	6.4 (4.8, 7.9)	6.9 (5.1, 8.8)	7.6 (5.9, 9.3)
Presence of anxiety only	6.3 (3.3, 9.1)	5.4 (0.2, 10.7)	4.9 (0.3, 9.5)	6.5 (0.3, 12.7)	7.9 (1.3, 14.9)
Presence of depression only	9.6 (5.2, 14.1)	4.7 (0.5, 10.4)	5.7 (0.45, 13.4)	13.3 (3.0, 23.2)	14.1 (2.7, 25.3)
Presence of both anxiety and depression	10.0 (6.8, 13.1)	1.4 (0.1, 4.2)	8.0 (1.9, 14.1)	15.9 (6.3, 25.6)	15.7 (9.5, 23.2)

[a]Adjusted for parity, ethnicity, and body mass index, maternal age, smoking, social support, maternal education, and household total income; [b]quintile 1: least deprived neighborhood; [c]quintile 5: most deprived neighborhood (quintile 4 and 5 were combined due to few or no cases in some strata); OR: odds ratio; CI: confidence interval

Figure 1: A directed acyclic graph depicting the hypothesized causal structure connecting anxiety and depression to preterm birth*



*The same causal structure is hypothesized to apply both to low and high SES neighborhoods. Maternal age and SES are considered causes of maternal BMI, which is therefore a collider variable in the causal model. However, simultaneous adjustment for age and maternal SES block the biasing paths opened by adjustment for maternal BMI

Ⓔ: exposure; ⓞ: outcome; ◯: adjusted; SES: socioeconomic status; BMI: body mass index

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4, and 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6 and 7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7 and 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7 and 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9, 10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9, 10
Bias	9	Describe any efforts to address potential sources of bias	8, 9, 10
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9, 10
		(*b*) Describe any methods used to examine subgroups and interactions	9, 10
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	12

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Not provided now: can be provided if requested
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, 11, 12, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	10, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11, Table 2 and 3
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not done
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11 and Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13, 14, 15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17, 18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.