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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-031035
Article Type:	Research
Date Submitted by the Author:	12-Apr-2019
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Keywords:	MENTAL HEALTH, EPIDEMIOLOGY, Preterm birth, Neighbourhood socioeconomic status

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4 **Neighborhood socioeconomic status modifies the association between anxiety and**
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6 **depression during pregnancy and preterm birth: A Community-based Canadian Cohort**
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8 **Study**
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Word Count: 3000

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Abstract

Background

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

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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

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2
3 income, education, and employment status) at a certain geographical level.(16) Neighborhood
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5 SES may influence the risk of PTB by exposing women to health benefitting or risk elevating
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7 factors.(16-19) Low neighborhood SES may affect an individual's ability to fulfill daily needs,
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9 access resources, make lifestyle choices, and cope with different situations.(16-19) Thus, the risk
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11 of PTB that is associated with anxiety and/or depression during pregnancy may differ by
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13 neighborhood SES. To our knowledge, this has not been examined.
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17 This study examined the association of the presence of anxiety symptoms alone,
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19 depression symptoms alone, and both anxiety and depression symptoms with PTB. This study
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21 further examined whether the presence of anxiety, depression, and both anxiety and depression
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23 interact with neighborhood SES to increase the risk of PTB. This may help to determine the
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25 subgroups of women who are at increased risk for PTB.
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30 31 **METHODS**

32 33 **Data sources**

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35 This study combined datasets from two community-based prospective pregnancy cohort
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37 studies in Alberta, Canada (n=5,528). The All Our Families (AOF) cohort study recruited 3,341
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39 pregnant women and the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort study
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41 recruited 2,187 pregnant women, with 231 women participating in both studies. Both studies
42
43 collected data on socio-demographics, lifestyle, social support, anxiety, depression, and PTB.
44
45 (20) The description and comparability of these two cohort studies is available elsewhere,(20,
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47 21) and justifies combining these data sources.(22) Briefly, each cohort study had similar
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49 recruitment periods (2008-2012), inclusion criteria, sampling design, and data-collection
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51 methods.(25, 26) We obtained two de-identified cohort datasets linked with neighborhood SES
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3 data from SAGE (Secondary Analysis to Generate Evidence), the secure data repository
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5 developed by PolicyWise for Children & Families, which houses these datasets. Ethics approval
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7 for this study was obtained from the Conjoint Health Research Ethics Board at the University of
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10 Calgary.

11 12 **Patient and public involvement**

13
14 This study used de-identified secondary data. Patient and public were not involved in this
15
16 study.
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18 19 **Variables**

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21 Variables that were deemed similar in the two studies were harmonized and appended
22
23 into a single new dataset. Women who participated in both studies (n=231) were counted only
24
25 once. Both cohorts used an identical measure of depression, i.e., the Edinburgh Depression Scale
26
27 (EPDS). The EDS is a 10-item self-reported scale with each item ranging from 0 to 3 to assess
28
29 symptoms of current depression (i.e. how women have felt in the past 7 days).(23) The EDS has
30
31 high internal consistency of 0.87,(23) a sensitivity of 78%, and specificity of 99% in the obstetric
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33 population,(24, 25) and is the most common scale used to measure antenatal and postnatal
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35 depression.(26) The recommended standard cut-off score of ≥ 13 out of 30 points on the EPDS
36
37 was used to define the presence of clinically significant depression during pregnancy.(27) While
38
39 the EPDS was specifically designed to assess depression, three items (namely items 3, 4, and 5)
40
41 comprising the anxiety subscale (EDPS-3A) have been suggested as a measure of anxiety.(28,
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43 29) with a sensitivity of 66.7% and specificity of 88.2% in the obstetric population.(29)The
44
45 standard cut-off of ≥ 6 out of a maximum of 9 is used to define the presence of clinically
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47 significant anxiety during pregnancy.(29) The cohort studies used different measures of anxiety:
48
49 the AOF study used the State-Trait Anxiety Inventory and the APrON study used the Symptoms
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3 Checklist 90. Thus, the EDPS-3A was chosen as a measure of anxiety to have a consistent
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5 measure across studies and to avoid the introduction of misclassification bias related to the use of
6
7 different tools. Presence of both anxiety and depression was defined as meeting both anxiety and
8
9 depression definitions at the same time point in pregnancy. The birth that occurred before the 37
10
11 weeks of gestation was defined as PTB (both spontaneous and iatrogenic included).
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15 Neighborhood SES data were measured by the Pampalon material deprivation index
16
17 (derived from the 2011 Statistics Canada census).(30, 31) which was aggregated at the
18
19 dissemination area (DA) level. DA is the smallest geographical unit available in the Canadian
20
21 census, consisting of 400-700 persons.(32) The Pampalon material deprivation index is a
22
23 composite measure of neighborhood SES that combines the proportion of persons without high
24
25 school diplomas, the average personal income, and the rate of unemployment within the DA. It is
26
27 used as a quintile, with quintile 1 representing the least deprived and quintile 5 representing the
28
29 most deprived neighborhoods.(30)
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32 33 **Data Analysis**

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35 First, variables significantly associated with PTB as well as anxiety and depression were
36
37 identified using bivariate analysis ($p < 0.05$). Then, a multivariable logistic regression model for
38
39 the association between anxiety and/or depression (“anxiety only,” “depression only,” and “both
40
41 anxiety and depression”) and PTB was constructed. The model included variables identified in
42
43 the bivariate analysis (parity, ethnicity, and body mass index), other variables (smoking, social
44
45 support, and maternal SES: these variables were selected based on literature, considering that
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47 they may influence the association in the multivariable model), and interaction terms. The
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49 interaction terms comprised “anxiety only,” “depression only,” and “both anxiety and
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51 depression” combined with each quintile of deprivation indices. Quintile 4 and 5 were combined
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3 as there were few or no cases in some strata. The presence of significant interactions was
4 identified through the p-values associated with beta coefficients of each interaction term.
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8 Variables were dropped from the model using a stepwise backward variable elimination
9 approach if they did not influence the association between anxiety and/or depression and PTB.
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11 The interaction terms and variables (parity, ethnicity, and body mass index) were retained in the
12 model as some of the interaction terms were significant and the variables influenced the
13 association. This approach (limiting the variables in the model) adjusted for confounding and
14 improved the precision of the estimates. Subsequently, we constructed another model without the
15 interaction terms. A likelihood ratio test was used to compare the goodness of model fit between
16 those two nested models – with and without the interaction terms. Adjusted prediction of PTB
17 (i.e., predicted probability of PTB that was evaluated at the average value of covariates, parity,
18 ethnicity, and body mass index, across observations) was estimated using the model with
19 interaction terms. Missing data were deleted using variable-wise or pair-wise deletion approach
20 for univariate or bivariate analysis and listwise deletion approach for regression models. Alpha
21 (α) of <0.05 was used to determine statistical significance. All analyses were performed using
22 STATA/IC 14.1.
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42 **RESULTS**

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44 Of total 5,297 pregnant women, the proportion of missing data ranged from 1.5% for
45 depression to 7.5% for gestational age at delivery. Overall, 7.3% (95% CI=6.6, 8.1) of women
46 delivered preterm infants. Women who delivered preterm infants were more likely to be non-
47 white, obese, primiparous, and from the most deprived neighborhoods. As shown in Table 1,
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49 17.9% of women had anxiety and/or depression: 7.7% (95% CI=7.0, 8.4) of women had both
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3 anxiety and depression, followed by 6.0% (95% CI=5.4, 6.6) women had anxiety alone, and
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5 4.2% (95% CI=3.7, 4.8) women had depression alone. Women with both anxiety and depression
6
7 had a higher rate of PTB (10.6%, 95% CI=7.8, 14.3) compared to those with isolated anxiety
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9 (6.5%, 95% CI=4.2, 10.0) or isolated depression (8.2%, 95% CI=5.1, 12.9) or without anxiety
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11 and depression (6.9%, 95% CI=6.1, 7.7). A higher proportion of women with a presence of both
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13 anxiety and depression (compared to those with anxiety or depression alone) were single, non-
14
15 white, recent immigrants, had a low household income, and were from the most deprived
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17 neighborhoods ($p<0.05$) (Table 1). Mean scores of anxiety (6.6 ± 0.4) and depression (16.2 ± 0.13)
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19 were higher among women with both conditions compared to those with anxiety alone (6.1 ± 0.2)
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21 or depression alone (14.6 ± 0.12).
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26 The presence of both anxiety and depression (adjusted odds ratio (aOR)=1.6, 95%
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28 CI=1.1, 2.3), but neither anxiety alone (aOR=0.9, 95% CI=0.5, 1.4) nor depression alone
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30 (aOR=1.3, 95% CI=0.8, 2.2), was significantly associated with PTB (Table 2). Effect
31
32 modification was observed between the presence of both anxiety and depression and
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34 neighborhood SES (specifically, neighborhood with deprivation quintile 4 and 5 combined, p -
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36 value=0.014, and deprivation quintile 3, p -value=0.015). Compared to women without anxiety
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38 and depression, women with both anxiety and depression who lived in quintile 3 and more
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40 deprived neighborhoods had significantly increased odds of experiencing a preterm delivery
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42 (quintile 4 and 5: aOR=2.3, 95% CI=1.3, 4.1). Whereas, compared to women without anxiety
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44 and depression, women with both anxiety and depression who lived in the least deprived
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46 neighborhood were not at elevated odds of experiencing a preterm delivery (aOR=0.2, 95 %
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48 CI=0.01, 1.3) (Table 2).
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3 As shown in Table 3, the predicted probability of PTB for women with a presence of both
4 anxiety and depression was 10.0% (95% CI=6.8, 13.1). It increased to 15.7% (95% CI=9.5, 22.6)
5
6 if they lived in the most deprived neighborhoods – an increase of 57.1% – and it decreased to
7
8 1.4% (95% CI=0.04, 4.2) if they lived in the least deprived neighborhoods. The predicted
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10 probability of PTB for women with depression alone was 9.6% (95% CI=5.2, 14.1), which
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12 increased to 14.0% (95% CI=2.7, 25.3) if they lived in the most deprived neighborhoods. The
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14 predicted probability for women with anxiety alone and women with absence of anxiety and
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16 depression remained similar across the neighborhood deprivation indices.
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24 **DISCUSSION**

25 **Main findings**

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27 This study examined the association of anxiety alone, depression alone, and the presence
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29 of both anxiety and depression during pregnancy with PTB, using data from two community-
30
31 based pregnancy cohort studies in Alberta, Canada. The study found an association between the
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33 presence of both anxiety and depression and PTB, which significantly differed according to
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35 neighborhood SES. Women with both anxiety and depression were more likely to deliver
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37 preterm infants if they lived in a relatively more deprived neighborhood compared to if they
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39 lived in a less deprived neighborhood. For women with both anxiety and depression, the absolute
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41 predicted probability of delivering preterm infants was 16% if these women lived in the most
42
43 deprived neighborhood and it was 1% if they lived in the least deprived neighborhood. Overall,
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45 the findings suggest the importance of neighborhoods on maternal health (in general) and more
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47 specifically preterm birth.
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53 **Interpretation**

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3 Although few previous studies assessed the association between the presence of both
4 anxiety and depression during pregnancy and PTB, our finding is consistent with their findings
5 that the presence of both anxiety and depression increases the risk of PTB.(14, 33, 34) This may
6 be related to the additive effects of prenatal depression and anxiety and the effects of severity of
7 anxiety and depressive symptoms. Previous studies conducted in the general population and in
8 pregnant women found a higher score of anxiety or depression symptoms among those with both
9 anxiety and depression than those with isolated anxiety or depression.(34, 35) – the findings are
10 consistent with our findings. It is also reported in previous studies that individuals with both
11 anxiety and depression have longer depressive episodes, worse psychosocial impairment, poorer
12 response to medication, compromised quality of life, and increased suicidality than those with
13 isolated anxiety or depression.(12, 33, 35) Thus, the presence of both anxiety and depression
14 during pregnancy may lead to an increased risk of poor birth outcomes, including PTB, than
15 depression or anxiety alone.
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33 Our study did not find an association between anxiety alone or depression alone and
34 PTB, which is consistent with previous studies that analyzed isolated anxiety or depression
35 separately from the presence of both or comorbid anxiety and depression.(14, 34) However, the
36 finding is inconsistent with several previous studies that analyzed anxiety or depression
37 intermixing with the presence of both conditions.(8, 10) It is possible that the association
38 described in the literature requires high levels of anxiety or depression, which is more likely
39 present in the presence of both anxiety and depression symptoms or disorders. Thus, the
40 associations found in previous studies may have been confounded by the presence of both
41 anxiety and depression symptoms or comorbid anxiety and depression disorders. The increased
42 risk of PTB associated with the presence of both anxiety and depression (but not with isolated
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3 anxiety or depression) may, in part, explain the inconsistencies across previous findings on the
4 association between prenatal anxiety or depression and PTB. Similarly, previous studies did not
5 analyze the association stratified by neighborhood SES, meaning that these studies averaged the
6 association across neighborhood SES, which may also explain the inconsistencies across
7 previous studies findings.
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14 A strong association between the presence of both anxiety and depression and PTB
15 among women living in a relatively more deprived neighborhood may reflect that, besides
16 individual level risk factors, the risk of PTB is related to neighborhood factors.(16-18) For
17 example, women living in deprived neighborhoods often have less access to healthy foods,
18 quality health services, and opportunities for leisure activity, and have more exposure to societal
19 stressors and crimes.(16-19) Anxious and depressed women living in less advantaged areas may
20 interpret the deprivation associated stressors more acutely and have less support or are less able
21 to manage or cope with their stressors, making them severely emotionally distressed compared to
22 those living in more advantaged areas.(8, 11, 36, 37) Consequently, the elevated risk of
23 delivering preterm is more likely to occur in this group of women. However, it is important to
24 note that, the relationship between mental illness and impoverishment is difficult to interpret as
25 causal, given the bi-directional relationship between them. Furthermore, in our study, the group
26 of women with both anxiety and depression (who often have severe symptoms of anxiety or
27 depression) in the least deprived neighborhoods had exceptionally low rate of PTB. The
28 observed association between the presence of both anxiety and depression and PTB among
29 women living in a relatively more deprived neighborhood seems to depend on this result. Thus,
30 the replication of this finding seems important.
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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

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2
3 PTB analyzing the influence of several potential confounders, other confounders such as
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5 antidepressant use, other psychiatric conditions, and medical risk factors that may influence the
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7 associations were not considered due to data limitation. Similarly, we were not able to separate
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9 out spontaneous and iatrogenic PTB in the model – the association might be stronger with a
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11 focus on spontaneous PTB. Overall, replication of this study addressing these limitations may
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13 further the understanding on risk factors and preventive strategies of PTB.
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16 17 **Conclusions**

18
19 Our study found that the presence of both prenatal anxiety and depression increases the
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21 risk of PTB and the risk is higher for women living in low SES neighborhoods compared to
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23 women living in high SES neighborhoods. The finding informs that an intervention strategy that
24
25 focuses on a group of women with a presence of both anxiety and depression and living in the
26
27 most deprived neighborhood may reduce the risk of PTB. Furthermore, future research that
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29 examines the influence of severity of anxiety and depression on risk of PTB may further the
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31 understanding on risk factors and preventive strategies of PTB. A strategy that identifies and
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33 manages anxiety and depression prior to pregnancy should be a priority.
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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

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3 Alberta Innovates to conduct this study. The funding agencies have no role in study design, data
4 access, analysis, and interpretation, manuscript writing, and in the decision to submit the article
5 for publication.
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10 11 12 **Data sharing**

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14 Additional data such as statistical codes, supplementary tables, and technical appendix are
15 available upon request (by emailing Kamala Adhikari: kamala.adhikaridahal@ucalgary.ca)
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20 21 22 **Ethical statements**

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24 Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at
25 the University of Calgary (REB16-2548_REN1). This study used secondary data and all the data
26 were anonymized; therefore, did not require informed consent.
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31 32 33 **Competing interests**

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35 The authors declare that they have no competing interests.
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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%)	χ^2 p-value
	n (%), 95% CI)	n (%), 95% CI)	n (%), 95% CI)	n (%), 95% CI)	
Maternal age ≥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)	0.006
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 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)	<0.0001
Duration of stay in Canada Born/5 years+ <5 years	3841 (91.6, 90.7-92.4) 352 (8.4, 7.6-9.3)	275 (89.9, 85.9-92.8) 31 (10.1, 7.2-14.1)	185 (87.3, 82.1-91.1) 27 (12.7, 8.9-17.9)	329 (84.4, 80.4-87.6) 61 (15.6, 12.4-19.6)	<0.0001
Body mass index Underweight (<18.5kg/m ²) Normal weight (18.5 - 24.99 kg/m ²) Overweight (25 - 29.99 kg/m ²) Obesity (≥30 kg/m ²)	170 (4.2, 3.6-4.9) 2552 (63.2, 61.7-64.7) 882 (21.9, 20.6-23.1) 432 (10.7, 9.8-11.7)	12 (4.1, 2.3-7.1) 172 (58.5, 52.8-64.0) 59 (20.1, 15.9-25.0) 51 (17.4, 13.4-22.1)	11 (5.3, 2.9-9.3) 125 (59.8, 53.0-66.2) 50 (23.9, 18.6-30.2) 23 (11.0, 7.4-16.0)	21 (5.6, 3.7-8.4) 220 (58.4, 53.3-63.2) 73 (19.4, 15.7-23.7) 63 (16.7, 13.3-20.8)	0.002
Parity 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)	<0.0001
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 High school or less than high school Some post-secondary Completed post-secondary	451 (10.6, 9.7-11.6) 669 (15.8, 14.7-16.9) 3121 (73.6, 72.2-74.9)	49 (16.2, 12.5-20.8) 57 (18.9, 14.8-23.7) 196 (64.9, 59.4-70.1)	42 (19.4, 14.7-25.3) 35 (16.2, 11.9-21.7) 139 (64.4, 57.7-70.5)	68 (17.3, 13.9-21.4) 96 (24.4, 20.4-28.9) 229 (58.3, 53.3-63.1)	<0.0001

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%)	χ^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)

^aAdjusted for parity, ethnicity, and body mass index; ^babsence of both anxiety and depression as a reference group; ^cquintile 1: least deprived neighborhood; ^dquintile 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)

^aAdjusted for parity, ethnicity, and body mass index; ^bquintile 1: least deprived neighborhood; ^cquintile 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.

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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.

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BMJ Open

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

Journal:	<i>BMJ Open</i>
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 Metcalf, 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

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4 **Neighborhood socioeconomic status modifies the association between anxiety and**
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6 **depression during pregnancy and preterm birth: A Community-based Canadian Cohort**
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8 **Study**
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Word Count: 3604

For peer review only

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

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3 (OR=1.6, 95% CI=1.1, 2.3) and had significant interaction with neighborhood deprivation (p-
4 value=0.004). The predicted probability of PTB for women with both anxiety and depression
5 was 10.0%, which increased to 15.7% if they lived in the most deprived neighborhoods and
6 decreased to 1.4% if they lived in the least deprived neighborhoods.
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14 **Conclusions:** Effects of anxiety and depression on risk of PTB differ depending on where
15 women live. This understanding may guide the identification of women at increased risk for PTB
16 and allocation of resources for early identification and management of anxiety and depression.
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24 **Keywords:** anxiety and depression, neighborhood socioeconomic status, deprivation, preterm
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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

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3 income, education, and employment status) at a certain geographical level.(16) Neighborhood
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5 SES may influence the risk of PTB by exposing women to health benefitting or risk elevating
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7 factors, such as access to healthy foods, quality health services, opportunities for leisure activity,
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9 and social support and exposure to societal stressors, crimes, and poor air and water quality.(16-
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11 19) Low neighborhood SES may affect an individual's ability to fulfill daily needs, access
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13 resources, make lifestyle choices, and cope with different situations.(16-19) Thus, the risk of
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15 PTB that is associated with anxiety and/or depression during pregnancy may differ by
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17 neighborhood SES. To our knowledge, this has not been examined.
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22 This study examined the association of the presence of anxiety symptoms alone,
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24 depression symptoms alone, and both anxiety and depression symptoms with PTB. This study
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26 further examined whether the presence of anxiety, depression, and both anxiety and depression
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28 interact with neighborhood SES to increase the risk of PTB. This may help to determine the
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30 subgroups of women who are at increased risk for PTB.
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35 **METHODS**

36 **Data sources**

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40 This study combined datasets from two community-based prospective pregnancy cohort
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42 studies in Alberta, Canada (n=5,528). The All Our Families (AOF) cohort study recruited 3,341
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44 pregnant women and the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort study
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46 recruited 2,187 pregnant women, with 231 women participating in both studies. The description
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48 and comparability of these two cohort studies is available elsewhere,(20, 21) and justifies
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50 combining these data sources.(22) The AOF study aimed to examine maternal well-being and
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52 infant outcomes and the APrON study aimed to investigate the role of prenatal maternal nutrition
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3 on maternal mental health and infant outcomes.(20, 21) Briefly, each cohort study had similar
4 inclusion criteria, sampling design (community-based, non-stratified sampling), and data
5 collection methods.(21) Both studies recruited pregnancy cohorts between 2008 and 2012 from
6 maternity clinics, high schools, public places, etc. and followed them up. The follow-up for
7 mother and child dyad is still ongoing in both studies.(21)
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14 We obtained two de-identified cohort datasets linked with neighborhood SES data from
15 SAGE (Secondary Analysis to Generate Evidence), the secure data repository developed by
16 PolicyWise for Children & Families, which houses these datasets. Ethics approval for this study
17 was obtained from the Conjoint Health Research Ethics Board at the University of Calgary.
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24 **Patient and public involvement**

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

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32 Variables that were deemed similar in the two studies were harmonized and appended
33 into a single new dataset. Women who participated in both studies (n=231) were counted only
34 once. Data on age, ethnicity (white includes all Caucasians and non-white includes all non-
35 Caucasians), maternal SES, parity, BMI, smoking status, social support, depression, and anxiety
36 were collected at <27 weeks of gestation (in the APrON study) and at <25 weeks of gestation (in
37 the AOF study). BMI was calculated based on the self-reported pre-pregnancy height and weight
38 (i.e., immediately before pregnancy). Additionally, depression and anxiety were measured during
39 the third trimester (APrON: 27-42 weeks of gestation; AOF: 34-36 weeks of gestation).(20, 21)
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51 Both cohorts used an identical measure of depression, i.e., the Edinburgh Depression
52 Scale (EPDS). The EPDS is a 10-item self-reported scale with each item ranging from 0 to 3 to
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3 assess symptoms of current depression (i.e. how women have felt in the past 7 days).(23) The
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5 EPDS has high internal consistency of 0.87,(23) a sensitivity of 78%, and specificity of 99% in
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7 the obstetric population,(24, 25) and is the most common scale used to measure antenatal and
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9 postnatal depression.(26) The recommended standard cut-off score of ≥ 13 out of 30 points on the
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11 EPDS was used to define the presence of clinically significant depression during pregnancy.(27)
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13 While the EPDS was specifically designed to assess depression, three items (namely items 3, 4,
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15 and 5) comprising the anxiety subscale (EDPS-3A) have been suggested as a measure of anxiety
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17 by previous studies,(28, 29) with a sensitivity of 66.7% and specificity of 88.2% in the obstetric
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19 population.(29)The standard cut-off of ≥ 6 out of a maximum of 9 is used to define the presence
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21 of clinically significant anxiety during pregnancy.(29) The cohort studies used different
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23 measures of anxiety: the AOF study used the State-Trait Anxiety Inventory and the APrON study
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25 used the Symptoms Checklist 90. Thus, the EDPS-3A was chosen as a measure of anxiety to
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27 have a consistent measure across studies and to avoid the introduction of misclassification bias
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29 related to the use of different tools. Presence of isolated anxiety or depression was defined as
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31 meeting the anxiety or depression definition during pregnancy. Presence of both anxiety and
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33 depression was defined as meeting both anxiety and depression definitions at the same time point
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35 in pregnancy. Births that occurred before 37 weeks of gestation were defined as PTB (both
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37 spontaneous and iatrogenic included). PTB was measured at 4 months of postpartum period
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39 based on maternal recall of week of gestation at delivery.
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47 Neighborhood SES data were measured by the Pampalon material deprivation index
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49 (derived from the 2011 Statistics Canada census)(30, 31) which was aggregated at the
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51 dissemination area (DA) level. DA is the smallest geographical unit available in the Canadian
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53 census, consisting of 400-700 persons.(32) The Pampalon material deprivation index is a
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3 composite measure of neighborhood SES that combines the proportion of persons without high
4 school diplomas, the average personal income, and the rate of unemployment within the DA. It is
5 used as a deprivation quintile, with quintile 1 representing the least deprived and quintile 5
6 representing the most deprived neighborhoods.(30) Neighborhood SES was assigned to each
7 cohort based on their postal code of residence at the time of cohort recruitment.
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14 **Data Analysis**

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17 First, variables significantly associated with PTB as well as anxiety and/or depression
18 (“anxiety only,” “depression only,” and “both anxiety and depression”) were identified using
19 bivariate analysis ($p < 0.05$). The significantly associated variables were parity, ethnicity, and
20 body mass index. Then, a multivariable logistic regression model was constructed to examine the
21 association between anxiety and/or depression and PTB, adjusting for parity, ethnicity, and body
22 mass index. Smoking, social support, and maternal education and household income variables
23 were also initially selected based on literature to include in the multivariable model, considering
24 that they may change or confound the association between anxiety/depression and PTB in the
25 multivariable model. However, these variables did not change or confound the association in the
26 multivariable model and were thus dropped from the model.
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40 A multilevel multivariable logistic regression model, which assumes the lack of
41 independence of observations and accounts for the variation between groups or areas, was then
42 constructed to examine the effect modification of neighborhood SES on the association between
43 anxiety and/or depression and PTB. This model included interaction terms in addition to parity,
44 ethnicity, and body mass index. The interaction terms comprised “anxiety only,” “depression
45 only,” and “both anxiety and depression” combined with each quintile of deprivation indices.
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54 Deprivation quintile 4th and 5th were combined as there were few or no cases in some strata.
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3 The presence of significant interactions was identified through the p-values associated with beta
4 coefficients of each interaction term. Subsequently, we constructed another model without the
5 interaction terms. A likelihood ratio test was used to compare the goodness of model fit between
6 those two nested models – with and without the interaction terms. Adjusted prediction of PTB
7 (i.e., predicted probability of PTB that was evaluated at the average value of covariates, parity,
8 ethnicity, and body mass index, across observations) was estimated using the model with
9 interaction terms. Alpha (α) of <0.05 was used to determine statistical significance. All analyses
10 were performed using STATA/IC 14.1.
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21 **Missing Data**

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24 The proportion of missing data for gestational age at delivery (PTB) was 7.5%, for
25 neighborhood deprivation indices was 7.8%, and for body mass index was 6.8%. Other variables
26 had missing data $<5\%$, ranging from 1.3% for depression to 4.4% for household total income.
27 The missing data for these variables occurred due to maternal non-response. Characteristics of
28 groups of women (such as ethnicity, parity, BMI, neighborhood SES, anxiety and depression)
29 with and without missing data on PTB were compared to assess differences. Multiple imputation
30 was used to address with missing data on the three variables (i.e., PTB, body mass index, and
31 neighborhood deprivation indices) that had $\geq 5\%$ missing data. (33) Using STATA's "mi
32 Package", the multiple imputation process was carried out in three steps as recommended by
33 Rubin: imputation, analysis, and combination. (33, 34) The method assumes that the missing data
34 are missing at random and attempts to estimate a missing value within a plausible set of
35 values. (33, 34) The imputation values (i.e., a predictive distribution based on observed data)
36 were estimated using an imputation model (with imputation 50 times). (33, 34) The imputation
37 model included the variables that were significant with missing data (i.e., marital status, duration
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3 of stay in Canada, maternal education, and household total income, intended pregnancy,
4 smoking, alcohol consumption) as well as those that were utilized in the analysis model (i.e.,
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6 PTB, ethnicity, parity, BMI, neighborhood SES, anxiety and depression, and interaction terms).
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8 Sensitivity analysis was done to compare the estimates from the analyses based on multiple
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10 imputation and from the analysis restricted to complete case.
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17 RESULTS

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19 Of total 5,297 pregnant women, 17.9% of women had anxiety and/or depression: 7.7% of
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21 women had both anxiety and depression, followed by 6.0% women had anxiety alone, and 4.2%
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23 women had depression alone. Women with both anxiety and depression had a higher rate of PTB
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25 (10.6%) compared to those with isolated anxiety (6.5%) or isolated depression (8.2%) or without
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27 anxiety and depression (6.9%). A higher proportion of women with a presence of both anxiety
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29 and depression (compared to those with anxiety or depression alone) were single, non-white,
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31 recent immigrants, had a low household income, and were from the most deprived
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33 neighborhoods ($p<0.05$) (Table 1). Mean scores of anxiety (mean=6.6, standard deviation
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35 (SD)=0.4) and depression (mean=16.2, SD=0.13) were higher among women with both
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37 conditions compared to those with anxiety alone (mean=6.1, SD=0.2) or depression alone
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39 (mean=14.6, SD=0.12). As shown in Table 2, women who delivered preterm infants were more
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41 likely to be non-white, obese, primiparous, and from the most deprived neighborhoods. Maternal
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43 ethnicity, parity, BMI, neighborhood SES, anxiety, and depression were significantly associated
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45 with the presence of missing data on PTB.
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51 The presence of both anxiety and depression (adjusted odds ratio (aOR)=1.6, 95%
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53 CI=1.1, 2.3), but neither anxiety alone (aOR=0.8, 95% CI=0.5, 1.4) nor depression alone
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3 (aOR=1.3, 95% CI=0.8, 2.3), was significantly associated with PTB (Table 3). Effect
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5 modification was observed between the presence of both anxiety and depression and
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7 neighborhood SES (p-value=0.004). Compared to women without anxiety and depression,
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9 women with both anxiety and depression who lived in quintile 3 and more deprived
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11 neighborhoods had significantly increased odds of experiencing a preterm delivery (quintile 4
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13 and 5: aOR=2.2, 95% CI=1.3, 3.9). In contrast, compared to women without anxiety and
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15 depression, women with both anxiety and depression who lived in the least deprived
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17 neighborhood were not at elevated odds of experiencing a preterm delivery (aOR=0.2, 95 %
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19 CI=0.1, 1.5) (Table 3). The OR estimates from the analyses based on multiple imputation and
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21 from the analysis restricted to complete cases were similar, with some confidence intervals being
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23 slightly narrower in the multiple imputation analysis.
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29 As shown in Table 4, the predicted probability of PTB for women with a presence of both
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31 anxiety and depression was 10.0% (95% CI=6.8, 13.1). It increased to 15.7% (95% CI=9.5, 22.6)
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33 if they lived in the most deprived neighborhoods – an increase of 57.1% – and it decreased to
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35 1.4% (95% CI=0.1, 4.2) if they lived in the least deprived neighborhoods. The predicted
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37 probability of PTB for women with depression alone was 9.6% (95% CI=5.2, 14.1), which
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39 increased to 14.0% (95% CI=2.7, 25.3) if they lived in the most deprived neighborhoods. The
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41 predicted probability for women with anxiety alone and women with absence of anxiety and
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43 depression remained similar across the neighborhood deprivation indices.
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49 **DISCUSSION**

50 **Main findings**

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

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30 Although few previous studies assessed the association between the presence of both
31 anxiety and depression during pregnancy and PTB, our finding is consistent with their findings
32 that the presence of both anxiety and depression increases the likelihood of PTB.(14, 35, 36)
33 This may be related to the additive effects of prenatal depression and anxiety and the effects of
34 severity of anxiety and depressive symptoms. Previous studies conducted in the general
35 population and in pregnant women found a higher score of anxiety or depression symptoms
36 among those with both anxiety and depression than those with isolated anxiety or depression.(36,
37 37). It is also reported in previous studies that individuals with both anxiety and depression have
38 longer depressive episodes, worse psychosocial impairment, poorer response to medication,
39 compromised quality of life, and increased suicidality than those with isolated anxiety or
40 depression.(12, 35, 37) Thus, the presence of both anxiety and depression during pregnancy may
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3 lead to an increased risk of poor birth outcomes, including PTB, relative to depression or anxiety
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5 alone.
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8 Our study did not find an association between anxiety alone or depression alone and
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10 PTB, which is consistent with a previous pregnancy cohort study that analyzed isolated anxiety
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12 or depression separately from the presence of both or comorbid anxiety and depression.(36)
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14 However, the finding is inconsistent with several previous studies that analyzed anxiety or
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16 depression intermixing with the presence of both conditions.(8, 10) It is possible that the
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18 association described in the literature requires high levels of anxiety or depression, which is
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20 more likely present in the presence of both anxiety and depression symptoms or disorders. Thus,
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22 the associations found in previous studies may have been confounded by the presence of both
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24 anxiety and depression symptoms or comorbid anxiety and depression disorders. The increased
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26 risk of PTB associated with the presence of both anxiety and depression (but not with isolated
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28 anxiety or depression) may, in part, explain the inconsistencies across previous findings on the
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30 association between prenatal anxiety or depression and PTB. Similarly, previous studies did not
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32 analyze the association stratified by neighborhood SES, meaning that these studies averaged the
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34 association across neighborhood SES, which may also explain the inconsistencies across
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36 previous studies findings.
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42 A strong association between the presence of both anxiety and depression and PTB
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44 among women living in a relatively more deprived neighborhood may reflect that, besides
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46 individual level risk factors, PTB is related to neighborhood factors.(16-18) For example, women
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48 living in deprived neighborhoods often have less access to healthy foods, quality health services,
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50 and opportunities for leisure activity, and have more exposure to societal stressors and
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52 crimes.(16-19) Anxious and depressed women living in less advantaged areas may interpret the
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3 deprivation associated stressors more acutely and have less support or are less able to manage or
4 cope with their stressors, making them severely emotionally distressed compared to those living
5 in more advantaged areas.(8, 11, 38, 39) Consequently, the elevated risk of delivering preterm is
6 more likely to occur in this group of women. However, it is important to note that, the
7 relationship between mental illness and impoverishment is difficult to interpret as causal, given
8 the bi-directional relationship between them. Furthermore, in our study, the group of women
9 with both anxiety and depression (who often have severe symptoms of anxiety or depression) in
10 the least deprived neighborhoods had an exceptionally low rate of PTB. The observed
11 association between the presence of both anxiety and depression and PTB among women living
12 in a relatively more deprived neighborhood seems to depend on this result. Thus, the replication
13 of this finding seems important.

24 **Strengths and limitations**

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26 To our knowledge, few studies have directly examined the presence of both depressive
27 and anxious symptoms versus isolated depressive or anxious symptoms as risk factors of PTB,
28 and no studies have examined neighborhood SES as a modifier to the relationship between
29 anxiety and/or depression and PTB. This study is important given its focus on the commonest
30 psychological condition (i.e., comorbid anxiety and depression) and the importance of
31 identification of specific groups of women who may benefit the most from the preventive
32 interventions. This study used two community-based prospective pregnancy cohort studies. This
33 provided an opportunity to describe PTB across the several strata of anxiety, depression, and
34 both anxiety and depression and neighborhood SES in a relatively representative sample
35 (compared, for example, to a hospital- or clinic-based sample) of pregnant women. However,
36 even using the two cohorts, some strata had few cases of preterm infants, which may have led to
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3 the observed imprecise and/or insignificant estimates (specifically in a group with depression
4 alone). As these cohorts over-represent women with high SES,(21, 40, 41) it limits the
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6 generalizability of the findings to other demographic groups. While the use of prospective
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8 measurement of depression and anxiety reduces the chance of misclassifications due to recall
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10 bias, the use of self-reported anxiety and depression measurement scales may have introduced
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12 measurement inaccuracy. Specifically, the EPDS-3A scale has not been validated in a pregnant
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14 population and it tends to provide high false-positive results based on its validation on during the
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16 postpartum period.(28, 29) Furthermore, the EPDS-3A is a subscale of the EPDS. The standard
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18 cut-off point for the EPDS excluding the items of the EPDS-3A has not been established. While
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20 the use of a single scale may overestimate the presence of anxiety and/or depression, being able
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22 to identify combined anxiety and depression group using a single scale is advantageous as it
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24 facilitates for intervention design. While we examined the association between anxiety and/or
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26 depression and PTB analyzing the influence of several potential confounders, other confounders
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28 such as antidepressant use, other psychiatric conditions, and medical risk factors that may
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30 influence the associations were not considered since they were not available in the study's data
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32 sources. Similarly, we were not able to separate out spontaneous and iatrogenic PTB in the
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34 model – the association might be stronger for spontaneous PTB. Overall, replication of this study
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36 addressing these limitations may further the understanding on risk factors and preventive
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38 strategies of PTB.
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46 We defined neighborhoods using the smallest area (i.e., dissemination area) where people
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48 living in the smallest area are more likely to be similar for the outcomes, used multilevel analysis
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50 that accounts for area-level variation, and adjusted for individual level variables, an appropriate
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52 analytical approach for multilevel data. However, it is difficult to interpret the influence of
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3 neighborhood SES using area-based variables, where women living in the same area share the
4 same value for the variable. Individuals who live in the same area may also experience different
5 contextual influences from many other areal units, and the timing and duration in which
6 individuals experienced these contextual influences is also uncertain.
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12 **Conclusions**

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14 Our study found that the presence of both prenatal anxiety and depression increases the
15 likelihood of PTB and the effect of this combination is stronger for women living in low SES
16 neighborhoods compared to women living in high SES neighborhoods. The finding may help to
17 inform development of intervention strategies (such as timely screening and management of
18 anxiety and depression) that focus on the most deprived neighborhood. Furthermore, future
19 research that examines the influence of severity of anxiety and depression on risk of PTB may
20 further the understanding on risk factors and preventive strategies of PTB.
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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

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3 Alberta Innovates to conduct this study. The funding agencies have no role in study design, data
4 access, analysis, and interpretation, manuscript writing, and in the decision to submit the article
5 for publication.
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10 11 12 **Data sharing**

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14 Additional data such as statistical codes, supplementary tables, and technical appendix are
15 available upon request (by emailing Kamala Adhikari: kamala.adhikaridahal@ucalgary.ca)
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20 21 22 **Ethical statements**

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24 Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at
25 the University of Calgary (REB16-2548_REN1). This study used secondary data and all the data
26 were anonymized; therefore, did not require informed consent.
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30 31 32 33 **Competing interests**

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35 The authors declare that they have no competing interests.
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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%)	χ^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						<0.0001
Single/divorced/separated	262 (5.1)	168 (3.9)	22 (7.2)	25 (11.5)	47 (11.8)	
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%)	χ^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 (%)	χ^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)

^aEstimates were from analyses based on multiple imputation; ^bAbsence of both anxiety and depression as a reference group; ^cquintile 1: least deprived neighborhood; ^dquintile 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)

^aAdjusted for parity, ethnicity, and body mass index; ^bquintile 1: least deprived neighborhood; ^cquintile 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.

1
2 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE
3 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
4 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.
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BMJ Open

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

Journal:	<i>BMJ Open</i>
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 Metcalf, 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

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4 **Neighborhood socioeconomic status modifies the association between anxiety and**
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6 **depression during pregnancy and preterm birth: A Community-based Canadian Cohort**
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8 **Study**
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13 Kamala Adhikari¹, Scott B Patten¹, Tyler Williamson¹, Alka B Patel^{1,2}, Shahirose Premji³,
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Word Count: 3686

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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

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3 (OR=1.6, 95% CI=1.1, 2.3) and had significant interaction with neighborhood deprivation (p-
4 value=0.004). The predicted probability of PTB for women with both anxiety and depression
5 was 10.0%, which increased to 15.7% if they lived in the most deprived neighborhoods and
6 decreased to 1.4% if they lived in the least deprived neighborhoods.
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14 **Conclusions:** Effects of anxiety and depression on risk of PTB differ depending on where
15 women live. This understanding may guide the identification of women at increased risk for PTB
16 and allocation of resources for early identification and management of anxiety and depression.
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24 **Keywords:** anxiety and depression, neighborhood socioeconomic status, deprivation, preterm
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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

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3 income, education, and employment status) at a certain geographical level.(16) Neighborhood
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5 SES may influence the risk of PTB by exposing women to health benefitting or risk elevating
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7 factors, such as access to healthy foods, quality health services, opportunities for leisure activity,
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9 and social support and exposure to societal stressors, crimes, and poor air and water quality.(16-
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11 19) Low neighborhood SES may affect an individual's ability to fulfill daily needs, access
12
13 resources, make lifestyle choices, and cope with different situations.(16-19) Thus, the risk of
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15 PTB that is associated with anxiety and/or depression during pregnancy may differ by
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17 neighborhood SES. To our knowledge, this has not been examined.
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22 This study examined the association of the presence of anxiety symptoms alone,
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24 depression symptoms alone, and both anxiety and depression symptoms with PTB. This study
25
26 further examined whether the presence of anxiety, depression, and both anxiety and depression
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28 interact with neighborhood SES to increase the risk of PTB. This may help to determine the
29
30 subgroups of women who are at increased risk for PTB.
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35 **METHODS**

36 **Data sources**

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39 This study combined datasets from two community-based prospective pregnancy cohort
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41 studies in Alberta, Canada (n=5,528). The All Our Families (AOF) cohort study recruited 3,341
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43 pregnant women and the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort study
44
45 recruited 2,187 pregnant women, with 231 women participating in both studies. Women
46
47 contributed only one pregnancy in the cohort. Women who participated in both studies were only
48
49 counted once. The description and comparability of these two cohort studies is available
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51 elsewhere,(20, 21) and justifies combining these data sources.(22) The AOF study aimed to
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3 examine maternal well-being and infant outcomes and the APrON study aimed to investigate the
4 role of prenatal maternal nutrition on maternal mental health and infant outcomes.(20, 21)
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6 Briefly, each cohort study had similar inclusion criteria, sampling design (community-based,
7 non-stratified sampling), and data collection methods.(21) Both studies recruited pregnancy
8 cohorts between 2008 and 2012 using community-based recruitment strategies (such as face-to-
9 face recruitment in maternity clinics by research assistants or nurses and recruitment in public
10 places using posters, pamphlets, and brochures) and followed them up. The follow-up for mother
11 and child dyad is still ongoing in both studies.(21)
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21 We obtained two de-identified cohort datasets linked with neighborhood SES data from
22 SAGE (Secondary Analysis to Generate Evidence), the secure data repository developed by
23 PolicyWise for Children & Families, which houses these datasets. Ethics approval for this study
24 was obtained from the Conjoint Health Research Ethics Board at the University of Calgary.
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30 **Patient and public involvement**

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

38 Variables that were deemed similar in the two studies were harmonized and appended
39 into a single new dataset. Women who participated in both studies (n=231) were counted only
40 once. Data on age, ethnicity (white includes all Caucasians and non-white includes all non-
41 Caucasians), maternal SES, parity, body mass index (BMI), smoking status, social support,
42 depression, and anxiety were collected at <27 weeks of gestation (in the APrON study) and at
43 <25 weeks of gestation (in the AOF study). BMI was calculated based on the self-reported pre-
44 pregnancy height and weight (i.e., immediately before pregnancy). Additionally, depression and
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3 anxiety were measured during the third trimester (APrON: 27-42 weeks of gestation; AOF: 34-
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5 36 weeks of gestation).(20, 21)
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8 Both cohorts used an identical measure of depression, i.e., the Edinburgh Depression
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10 Scale (EPDS). The EPDS is a 10-item self-reported scale with each item ranging from 0 to 3 to
11
12 assess symptoms of current depression (i.e. how women have felt in the past 7 days).(23) The
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14 EPDS has high internal consistency of 0.87,(23) a sensitivity of 78%, and specificity of 99% in
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16 the obstetric population,(24, 25) and is the most common scale used to measure antenatal and
17
18 postnatal depression.(26) The recommended standard cut-off score of ≥ 13 out of 30 points on the
19
20 EPDS was used to define the presence of clinically significant depression during pregnancy.(27)
21
22 While the EPDS was specifically designed to assess depression, three items (namely items 3, 4,
23
24 and 5) comprising the anxiety subscale (EDPS-3A) have been suggested as a measure of anxiety
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26 by previous studies,(28, 29) with a sensitivity of 66.7% and specificity of 88.2% in the obstetric
27
28 population.(29)The standard cut-off of ≥ 6 out of a maximum of 9 is used to define the presence
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30 of clinically significant anxiety during pregnancy.(29) The cohort studies used different
31
32 measures of anxiety: the AOF study used the State-Trait Anxiety Inventory and the APrON study
33
34 used the Symptoms Checklist 90. Thus, the EDPS-3A was chosen as a measure of anxiety to
35
36 have a consistent measure across studies and to avoid the introduction of misclassification bias
37
38 related to the use of different tools. Presence of isolated anxiety or depression was defined as
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40 meeting the anxiety or depression definition during pregnancy. Presence of both anxiety and
41
42 depression was defined as meeting both anxiety and depression definitions at the same time point
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44 in pregnancy. Births that occurred before 37 weeks of gestation were defined as PTB (both
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46 spontaneous and iatrogenic included). PTB was measured at 4 months of postpartum period
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48 based on maternal recall of week of gestation at delivery.
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3 Neighborhood SES data were measured by the Pampalon material deprivation index
4 (derived from the 2011 Statistics Canada census)(30, 31) which was aggregated at the
5 dissemination area (DA) level. DA is the smallest geographical unit available in the Canadian
6 census, consisting of 400-700 persons.(32) The Pampalon material deprivation index is a
7 composite measure of neighborhood SES that combines the proportion of persons without high
8 school diplomas, the average personal income, and the rate of unemployment within the DA. It is
9 used as a deprivation quintile, with quintile 1 representing the least deprived and quintile 5
10 representing the most deprived neighborhoods.(30) Neighborhood SES was assigned to each
11 cohort based on their postal code of residence at the time of cohort recruitment.
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24 **Data Analysis**

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26 Bivariate analysis was used to identify variables associated with PTB as well as anxiety
27 and/or depression (“anxiety only,” “depression only,” and “both anxiety and depression”). The
28 significantly associated ($p < 0.05$) variables were parity, ethnicity, and body mass index. A
29 multivariable logistic regression model was constructed to examine the association between
30 anxiety and/or depression and PTB. The model also included parity, ethnicity, BMI, maternal
31 age, smoking, social support, maternal education, and household total income variables. These
32 variables were selected to adjust for in the model based on our prior knowledge (or conceptual
33 understanding based on literature) that they are associated with both outcome (i.e., PTB) and
34 exposure (i.e., anxiety and/or depression) but do not reside in the causal pathway of the
35 relationship between anxiety and/or depression and PTB. The underlying hypothetical
36 relationship of the variables have been shown using a direct acyclic diagram (supplementary file:
37 Figure 1)
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53 A multilevel multivariable logistic regression model, which assumes the lack of
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3 independence of observations and accounts for the variation between groups or areas, was then
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5 constructed to examine the effect modification of neighborhood SES on the association between
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7 anxiety and/or depression and PTB. This model included interaction terms in addition to parity,
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9 ethnicity, BMI, maternal age, smoking, social support, maternal education, and household total
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11 income variables. The interaction terms comprised “anxiety only,” “depression only,” and “both
12
13 anxiety and depression” combined with each quintile of deprivation indices. Deprivation quintile
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15 4th and 5th were combined as there were few or no cases in some strata.
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19 The presence of significant interactions was identified through the p-values associated
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21 with beta coefficients of each interaction term. Subsequently, we constructed another model
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23 without the interaction terms. A likelihood ratio test was used to compare the goodness of model
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25 fit between those two nested models – with and without the interaction terms. Adjusted
26
27 prediction of PTB (i.e., predicted probability of PTB that was evaluated at the average value of
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29 covariates, parity, ethnicity, BMI, maternal age, smoking, social support, maternal education,
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31 and household total income variables, across observations) was estimated using the model with
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33 interaction terms. Alpha (α) of <0.05 was used to determine statistical significance. All analyses
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35 were performed using STATA/IC 14.1.
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39 40 **Missing Data**

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42 The proportion of missing data for gestational age at delivery (PTB) was 7.5%, for
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44 neighborhood deprivation indices was 7.8%, and for body mass index was 6.8%. Other variables
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46 had missing data <5%, ranging from 1.3% for depression to 4.4% for household total income.
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48 The missing data for these variables occurred due to maternal non-response. Characteristics of
49
50 groups of women (such as ethnicity, parity, BMI, neighborhood SES, anxiety and depression)
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52 with and without missing data on PTB were compared to assess differences. Multiple imputation
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3 was used to address with missing data on the three variables (i.e., PTB , body mass index, and
4 neighborhood deprivation indices) that had $\geq 5\%$ missing data .(33) Using STATA's "mi
5
6 Package", the multiple imputation process was carried out in three steps as recommended by
7
8 Rubin: imputation, analysis, and combination.(33, 34) The method assumes that the missing data
9
10 are missing at random and attempts to estimate a missing value within a plausible set of
11
12 values.(33, 34) The imputation values (i.e., a predictive distribution based on observed data)
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14 were estimated using an imputation model (with imputation 50 times).(33, 34) The imputation
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16 model included the variables that were significant with missing data (i.e., marital status, duration
17
18 of stay in Canada, intended pregnancy, alcohol consumption) as well as those that were utilized
19
20 in the analysis model (i.e., PTB, ethnicity, parity, BMI, maternal age, smoking, social support
21
22 maternal education, household total income, neighborhood SES, anxiety and depression, and
23
24 interaction terms). Sensitivity analysis was done to compare the estimates from the analyses
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26 based on multiple imputation and from the analysis restricted to complete case.
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35 RESULTS

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37 Of total 5,297 pregnant women, 17.9% of women had anxiety and/or depression: 7.7% of
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39 women had both anxiety and depression, followed by 6.0% women had anxiety alone, and 4.2%
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41 women had depression alone. Women with both anxiety and depression had a higher rate of PTB
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43 (10.6%) compared to those with isolated anxiety (6.5%) or isolated depression (8.2%) or without
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45 anxiety and depression (6.9%). A higher proportion of women with a presence of both anxiety
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47 and depression (compared to those with anxiety or depression alone) were single, non-white,
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49 recent immigrants, had a low household income, and were from the most deprived
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51 neighborhoods (p<0.05) (Table 1). Mean scores of anxiety (mean=6.6, standard deviation
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3 (SD)=0.4) and depression (mean=16.2, SD=0.1) were higher among women with both conditions
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5 compared to those with anxiety alone (mean=6.1, SD=0.2) or depression alone (mean=14.6,
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7 SD=0.1). As shown in Table 2, women who delivered preterm infants were more likely to be
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9 non-white, obese, primiparous, and from the most deprived neighborhoods. Variables such as
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11 maternal ethnicity, parity, BMI, neighborhood SES, anxiety, and depression were significantly
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13 associated with the presence of missing data on PTB.
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17 The presence of both anxiety and depression (adjusted odds ratio (aOR)=1.6, 95%
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19 CI=1.1, 2.3), but neither anxiety alone (aOR=0.8, 95% CI=0.6, 1.6) nor depression alone
20
21 (aOR=1.3, 95% CI=0.8, 2.5), was significantly associated with PTB (Table 3). Effect
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23 modification was observed between the presence of both anxiety and depression and
24
25 neighborhood SES (p-value=0.004). Compared to women without anxiety and depression,
26
27 women with both anxiety and depression who lived in quintile 3 and more deprived
28
29 neighborhoods had significantly increased odds of experiencing a preterm delivery (quintile 4
30
31 and 5: aOR=2.2, 95% CI=1.3, 4.0). In contrast, compared to women without anxiety and
32
33 depression, women with both anxiety and depression who lived in the least deprived
34
35 neighborhood were not at elevated odds of experiencing a preterm delivery (aOR=0.2, 95 %
36
37 CI=0.1, 1.5) (Table 3). The OR estimates from the analyses based on multiple imputation and
38
39 from the analysis restricted to complete cases were similar, with some confidence intervals being
40
41 slightly narrower in the multiple imputation analysis.
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47 As shown in Table 4, the predicted probability of PTB for women with a presence of both
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49 anxiety and depression was 10.0% (95% CI=6.8, 13.1). It increased to 15.7% (95% CI=9.5, 23.2)
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51 if they lived in the most deprived neighborhoods – an increase of 57.1% – and it decreased to
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53 1.4% (95% CI=0.1, 4.2) if they lived in the least deprived neighborhoods. The predicted
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3 probability of PTB for women with depression alone was 9.6% (95% CI=5.2, 14.1), which
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5 increased to 14.1% (95% CI=2.7, 25.3) if they lived in the most deprived neighborhoods. The
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7 predicted probability for women with anxiety alone and women with absence of anxiety and
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9 depression remained similar across the neighborhood deprivation indices.
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14 **DISCUSSION**

15 **Main findings**

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19 This study examined the association of anxiety alone, depression alone, and the presence
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21 of both anxiety and depression during pregnancy with PTB, using data from two community-
22
23 based pregnancy cohort studies in Alberta, Canada. The study found an association between the
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25 presence of both anxiety and depression and PTB, which significantly differed according to
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27 neighborhood SES. Women with both anxiety and depression were more likely to deliver
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29 preterm infants if they lived in a relatively more deprived neighborhood compared to if they
30
31 lived in a less deprived neighborhood. For women with both anxiety and depression, the absolute
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33 predicted probability of delivering preterm infants was 16% if these women lived in the most
34
35 deprived neighborhood and it was 1% if they lived in the least deprived neighborhood. Overall,
36
37 the findings suggest the importance of neighborhoods on maternal health (in general) and more
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39 specifically preterm birth.
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44 **Interpretation**

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47 Although few previous studies assessed the association between the presence of both
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49 anxiety and depression during pregnancy and PTB, our finding is consistent with their findings
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51 that the presence of both anxiety and depression increases the likelihood of PTB.(14, 35, 36)
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53 This may be related to the additive effects of prenatal depression and anxiety and the effects of
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3 severity of anxiety and depressive symptoms. Previous studies conducted in the general
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5 population and in pregnant women found a higher score of anxiety or depression symptoms
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7 among those with both anxiety and depression than those with isolated anxiety or depression.(36,
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9 37). It is also reported in previous studies that individuals with both anxiety and depression have
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11 longer depressive episodes, worse psychosocial impairment, poorer response to medication,
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13 compromised quality of life, and increased suicidality than those with isolated anxiety or
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15 depression.(12, 35, 37) Thus, the presence of both anxiety and depression during pregnancy may
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17 lead to an increased risk of poor birth outcomes, including PTB, relative to depression or anxiety
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19 alone.
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24 Our study did not find an association between anxiety alone or depression alone and
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26 PTB, which is consistent with a previous pregnancy cohort study that analyzed isolated anxiety
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28 or depression separately from the presence of both or comorbid anxiety and depression.(36)
29
30 However, the finding is inconsistent with several previous studies that analyzed anxiety or
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32 depression intermixing with the presence of both conditions.(8, 10) It is possible that the
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34 association described in the literature requires high levels of anxiety or depression, which is
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36 more likely present in the presence of both anxiety and depression symptoms or disorders. Thus,
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38 the associations found in previous studies may have been confounded by the presence of both
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40 anxiety and depression symptoms or comorbid anxiety and depression disorders. The increased
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42 risk of PTB associated with the presence of both anxiety and depression (but not with isolated
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44 anxiety or depression) may, in part, explain the inconsistencies across previous findings on the
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46 association between prenatal anxiety or depression and PTB. Similarly, previous studies did not
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48 analyze the association stratified by neighborhood SES, meaning that these studies averaged the
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3 association across neighborhood SES, which may also explain the inconsistencies across
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5 previous studies findings.
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8 A strong association between the presence of both anxiety and depression and PTB
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10 among women living in a relatively more deprived neighborhood may reflect that, besides
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12 individual level risk factors, PTB is related to neighborhood factors.(16-18) For example, women
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14 living in deprived neighborhoods often have less access to healthy foods, quality health services,
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16 and opportunities for leisure activity, and have more exposure to societal stressors and
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18 crimes.(16-19) Anxious and depressed women living in less advantaged areas may interpret the
19
20 deprivation associated stressors more acutely and have less support or are less able to manage or
21
22 cope with their stressors, making them severely emotionally distressed compared to those living
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24 in more advantaged areas.(8, 11, 38, 39) Consequently, the elevated risk of delivering preterm is
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26 more likely to occur in this group of women. However, it is important to note that, the
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28 relationship between mental illness and impoverishment is difficult to interpret as causal, given
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30 the bi-directional relationship between them. Furthermore, in our study, the group of women
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32 with both anxiety and depression (who often have severe symptoms of anxiety or depression) in
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34 the least deprived neighborhoods had an exceptionally low rate of PTB. The observed
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36 association between the presence of both anxiety and depression and PTB among women living
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38 in a relatively more deprived neighborhood seems to depend on this result. Thus, the replication
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40 of this finding seems important.
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46 **Strengths and limitations**

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49 To our knowledge, few studies have directly examined the presence of both depressive
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51 and anxious symptoms versus isolated depressive or anxious symptoms as risk factors of PTB,
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53 and no studies have examined neighborhood SES as a modifier to the relationship between
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3 anxiety and/or depression and PTB. This study is important given its focus on the commonest
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5 psychological condition (i.e., comorbid anxiety and depression) and the importance of
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7 identification of specific groups of women who may benefit the most from the preventive
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9 interventions. This study used two community-based prospective pregnancy cohort studies. This
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11 provided an opportunity to describe PTB across the several strata of anxiety, depression, and
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13 both anxiety and depression and neighborhood SES in a relatively representative sample
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15 (compared, for example, to a hospital- or clinic-based sample) of pregnant women. However,
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17 even using the two cohorts, some strata had few cases of preterm infants, which may have led to
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19 the observed imprecise and/or insignificant estimates (specifically in a group with depression
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21 alone). As these cohorts over-represent women with high SES,(21, 40, 41) it limits the
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23 generalizability of the findings to other demographic groups. While the use of prospective
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25 measurement of depression and anxiety reduces the chance of misclassifications due to recall
26
27 bias, the use of self-reported anxiety and depression measurement scales may have introduced
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29 measurement inaccuracy. Specifically, the EPDS-3A scale has not been validated in a pregnant
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31 population and it tends to provide high false-positive results based on its validation on during the
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33 postpartum period.(28, 29) Furthermore, the EPDS-3A is a subscale of the EPDS. The standard
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35 cut-off point for the EPDS excluding the items of the EPDS-3A has not been established. While
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37 the use of a single scale may overestimate the presence of anxiety and/or depression, being able
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39 to identify combined anxiety and depression group using a single scale is advantageous as it
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41 facilitates for intervention design. While we examined the association between anxiety and/or
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43 depression and PTB analyzing the influence of several potential confounders, other confounders
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45 such as antidepressant use, other psychiatric conditions, and medical risk factors that may
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47 influence the associations were not considered since they were not available in the study's data
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3 sources. Similarly, we were not able to separate out spontaneous and iatrogenic PTB in the
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5 model – the association might be stronger for spontaneous PTB. Overall, replication of this study
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7 addressing these limitations may further the understanding on risk factors and preventive
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9 strategies of PTB.
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12 We defined neighborhoods using the smallest area (i.e., dissemination area) where people
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14 living in the smallest area are more likely to be similar for the outcomes, used multilevel analysis
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16 that accounts for area-level variation, and adjusted for individual level variables, an appropriate
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18 analytical approach for multilevel data. However, it is difficult to interpret the influence of
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20 neighborhood SES using area-based variables, where women living in the same area share the
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22 same value for the variable. Individuals who live in the same area may also experience different
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24 contextual influences from many other areal units, and the timing and duration in which
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26 individuals experienced these contextual influences is also uncertain.
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30 31 **Conclusions**

32
33 Our study found that the presence of both prenatal anxiety and depression increases the
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35 likelihood of PTB and the effect of this combination is stronger for women living in low SES
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37 neighborhoods compared to women living in high SES neighborhoods. The finding may help to
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39 inform development of intervention strategies (such as timely screening and management of
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41 anxiety and depression) that focus on the most deprived neighborhood. Furthermore, future
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43 research that examines the influence of severity of anxiety and depression on risk of PTB may
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45 further the understanding on risk factors and preventive strategies of PTB.
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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

1
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3 Alberta Innovates to conduct this study. The funding agencies have no role in study design, data
4 access, analysis, and interpretation, manuscript writing, and in the decision to submit the article
5 for publication.
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10 11 12 **Data sharing**

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14 Additional data such as statistical codes, supplementary tables, and technical appendix are
15 available upon request (by emailing Kamala Adhikari: kamala.adhikaridahal@ucalgary.ca)
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20 21 22 **Ethical statements**

23
24 Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board at
25 the University of Calgary (REB16-2548_REN1). This study used secondary data and all the data
26 were anonymized; therefore, did not require informed consent.
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30 31 32 **Competing interests**

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34 The authors declare that they have no competing interests.
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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%)	χ^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						<0.0001
Single/divorced/separated	262 (5.1)	168 (3.9)	22 (7.2)	25 (11.5)	47 (11.8)	
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%)	χ^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 (%)	χ^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)

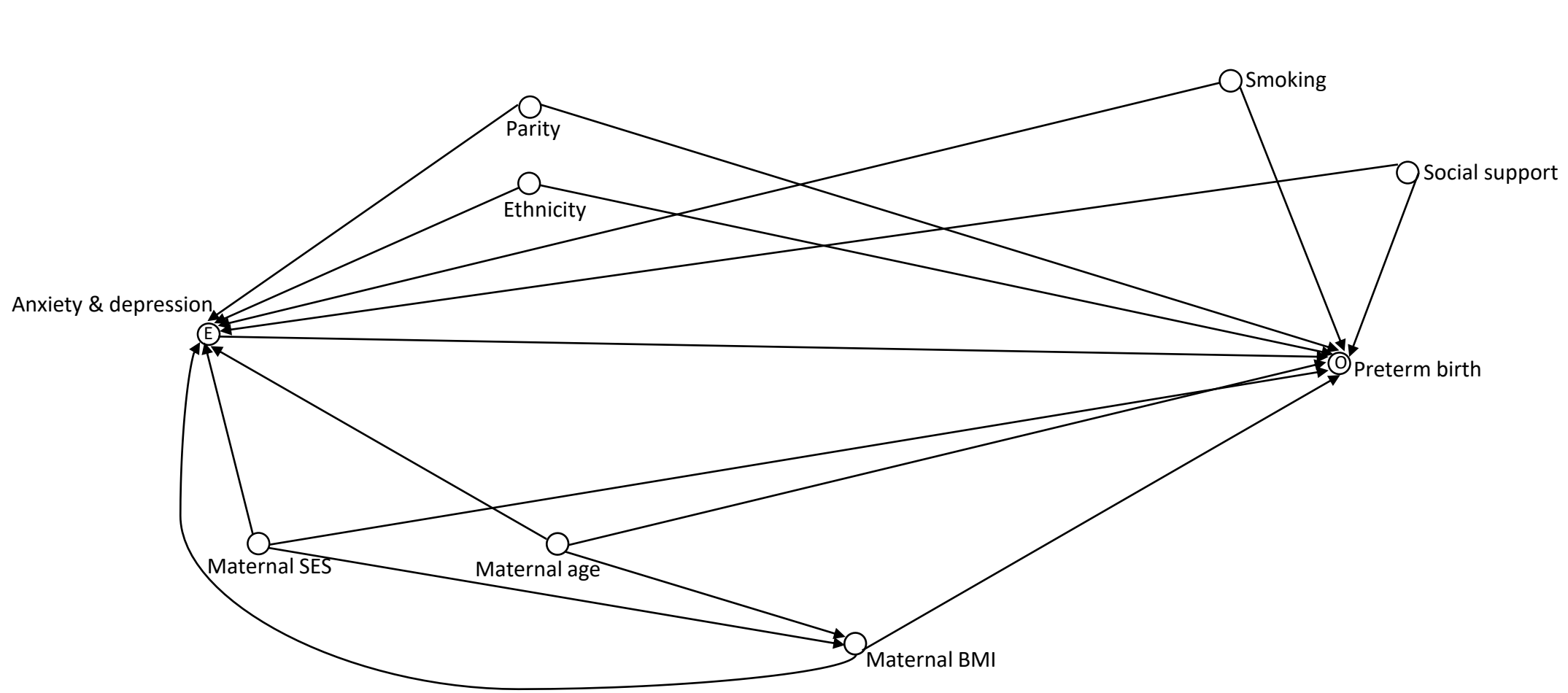
^aEstimates were from analyses based on multiple imputation; ^bAbsence of both anxiety and depression as a reference group; ^cquintile 1: least deprived neighborhood; ^dquintile 5: most deprived neighborhood (quintile 4 and 5 were combined due to few or no cases in some strata); OR: odds ratio; CI: confidence 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)

^aAdjusted for parity, ethnicity, and body mass index, maternal age, smoking, social support, maternal education, and household total income; ^bquintile 1: least deprived neighborhood; ^cquintile 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

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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.

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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.

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