Journal of Affective Disorders 227 (2017) 71–78

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Patterns of change in anxiety and depression during pregnancy predict preterm birth

Chelsea Doktorchik[a,*], Shahirose Premji[a,b,c], Donna Slater[c,d], Tyler Williamson[a,c,e], Suzanne Tough[a,c,f], Scott Patten[a,e,g]

[a] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, TRW Building 3rd Floor, 3280 Hospital Drive NW, Calgary, AB, Canada T2N 4Z6
[b] Faculty of Nursing, University of Calgary, 2500 University Drive NW, Calgary, AB, Canada T2N 1N4
[c] Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, Room 293 Heritage Medical Research Building, 3330 Hospital Drive NW, Calgary, AB, Canada T2N 4N1
[d] Departments of Physiology & Pharmacology and Obstetrics & Gynecology, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, Canada T2N 4N1
[e] O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, 3rd Floor TRW Building, 3280 Hospital Drive NW, Calgary, AB, Canada T2N 4Z6
[f] Department of Pediatrics, Cumming School of Medicine, University of Calgary, 2888 Shaganappi Trail NW, Calgary, AB, Canada T3B 6A8
[g] Department of Psychiatry, Cumming School of Medicine, University of Calgary, 1403 29th Street NW, Calgary, AB, Canada T2N 2T9

ARTICLE INFO

Keywords:
Pregnancy
Preterm birth
Anxiety
Depression
Chronic stress
Women's health

ABSTRACT

Background: To determine whether changes in anxiety and depression during pregnancy influence the risk of having a preterm birth (PTB), and whether chronic stress modifies this relationship.
Methods: The data source for the current study is the All Our Babies prospective cohort (AOB). Anxiety and depression were measured at 17–24 weeks and again at 32–36 weeks' gestation using the Spielberg State Anxiety Scale and the Edinburgh Postnatal Depression Scale, respectively. Chronic stress was assessed at 17–24 weeks' gestation as a potential covariate, and was measured using the Perceived Stress Scale. Multivariable logistic regression modeling was used to assess each relationship
Results: Women who experienced an increase in anxiety scores, (time point 32–36 weeks, compared to the earlier time point 17–24 weeks), had 2.70 times higher odds of preterm delivery, compared to those with a reduction in anxiety scores (95% CI 1.28, 5.69). Consistent low or high depression scores did not significantly influence the odds of PTB compared to a decrease in depression scores. A co-occurring increase in anxiety and depression scores was not found to increase the risk of PTB, and chronic stress did not modify any of these relationships.
Limitations: This study was limited by a relatively small sample of women who delivered preterm, and therefore it was not possible to conduct additional analyses. Further, the analyses were limited to mostly late preterm infants (32–36 weeks' gestation).
Conclusions: These findings should be validated with additional cohorts and a larger sample size. Ultimately, primary prevention could address anxiety during pregnancy.

1. Introduction

In Canada, approximately 8% of all live births are preterm, with Newfoundland and Labrador having the highest rate at 9%, and Alberta the second highest at 8.7% out of the Canadian provinces (Canadian Institute for Health Information, 2016). More importantly, 38% of infant mortality is due to preterm birth (PTB) (Public Health Agency of Canada, 2013), and the risk of having one or more morbidities increases as the gestational age at delivery decreases (Stoll et al., 2010). Worldwide, approximately 15 million infants are born prematurely per year (World Health Organization, 2012). Babies that survive a premature birth can face increased risk of challenges beyond infancy –

Abbreviations: PTB, Preterm Birth; AOB, All Our Babies; EPDS, Edinburgh Postnatal Depression Scale; PSS, Perceived Stress Scale; PPROM, Preterm Premature Rupture of the Membranes; OR, Odds Ratio; aOR, Adjusted Odds Ratio; HPA, Hypothalamic-Pituitary-Adrenocortical

* Corresponding author.
E-mail addresses: ctadokto@ucalgary.ca (C. Doktorchik), premjis@ucalgary.ca (S. Premji), dmslater@ucalgary.ca (D. Slater), tyler.williamson@ucalgary.ca (T. Williamson), stough@ucalgary.ca (S. Tough), patten@ucalgary.ca (S. Patten).

http://dx.doi.org/10.1016/j.jad.2017.10.001
Received 21 January 2017; Received in revised form 28 August 2017; Accepted 1 October 2017
Available online 02 October 2017
0165-0327/ © 2017 Elsevier B.V. All rights reserved.

neurodevelopmental sequelae such as cerebral palsy and delayed mental development, and various adult onset chronic diseases (e.g. cerebral palsy) which resulted from neurodevelopmental impairment (Institute of Medicine Committee, 2007). In addition to the risks for the premature infant, there are serious health consequences for maternal mental wellbeing. Mothers of preterm infants are at higher risk of postpartum depression than mothers of full-term infants, with prevalence of postpartum depression being as high as 40% (Brandon et al., 2011; Vigod et al., 2010). The financial burden of all preterm infants born in Canada for the first ten years of age equates to approximately $587 million due to healthcare utilization, medical costs, and mortality (Johnston et al., 2014). Consequently, there is a need to reduce the number of preterm deliveries and alleviate the negative consequences to the infant, their families, and society.

Anxiety and depression during pregnancy have been implicated as possible risk factors for PTB (Dayan et al., 2006; Ding et al., 2014; Dunkel Schetter and Tanner, 2012); however, findings are inconsistent. A meta-analysis conducted on depression and PTB revealed that only 25% of the studies analyzed found a significant association between depression during pregnancy and PTB (Accortt et al., 2015). Similarly, a meta-analysis examining maternal anxiety during pregnancy and PTB has also reported conflicting findings with anxiety and PTB (Rose et al., 2016). However, after a thorough analysis of these studies, Rose et al. concluded that these conflicting findings may be due to heterogeneity of the studies, including differing operationalization of anxiety, and assessing mental health only once and at differing times during pregnancy (Staneva et al., 2015). Measuring stress, anxiety, and depression as a combined construct during pregnancy was a superior predictor of PTB compared to measuring each dimension independently (Staneva et al., 2015). It is therefore important to measure anxiety and depression as co-occurring conditions.

During pregnancy, perception of stress and negative life events decline and physiological responses to stress diminish (Glynn et al., 2004), probably as a way to protect the mother and fetus from adverse health outcomes (Glynn et al., 2001). Chronic stress can result from ongoing, repetitive exposure to stressors, and is thought to alter the perception of anxiety and depression (Latendresse, 2009). Differing levels of chronic stress may heighten the perception of stressors, while reducing resiliency and the ability to cope (Chrousos, 1998; Dunkel Schetter and Dolbier, 2011; Latendresse, 2009). One can hypothesize that women who exhibit consistently high or increasing levels of anxiety or depression are at a greater risk of PTB. One study, however, measured the change in anxiety and perceived stress between two time points during pregnancy, and found an association between worsening perceived stress and anxiety, and an increased risk of PTB (Glynn et al., 2008). The results from Glynn et al. suggest that identifying patterns of anxiety and perceived stress during pregnancy may be a more accurate predictor of PTB than assessment at a single time point. It is therefore important to understand how a woman's psychosocial state can change and be modified throughout pregnancy, and how this may contribute to pregnancy outcomes, in the context of PTB. However, the study conducted by Glynn and colleagues did not consider how chronic stress might influence the relationship between anxiety and PTB, nor did it measure changes in depression during pregnancy to examine inter-relationships between anxiety and depression and how this influences PTB.

Allostatic load is a conceptual framework that describes the harmful physiological effects of chronic stress over time, and may explain the biological mechanisms behind PTB (McEwen and Seeman, 1999). Chronic stress can initiate a cascade of behavioral (e.g. smoking) and neuroendocrine (e.g. cortisol) responses which may negatively affect regular physiological systems, thereby increasing the susceptibility to disease or PTB (McEwen and Seeman, 1999). It is therefore important to consider chronic stress as a potential modifier when understanding the relationship between anxiety, depression, and PTB. Studies have not evaluated whether chronic stress modifies this relationship, which may explain the lack of consistency reported in the literature.

The current study aimed to determine: 1) the relationship between changes in anxiety and depression at two time points in pregnancy and the incidence of PTB, 2) whether a co-occurring increase in anxiety and depression scores increased the risk of delivering preterm, 3) whether important covariates, particularly chronic stress, modify this relationship, and 4) if changes in anxiety and depression during pregnancy differentially influence the risk, comparing PTB due to a medical indication or spontaneous preterm birth.

2. Methods

2.1. Study design

The data source for this study was the All our Babies (AOB) prospective cohort (McDonald et al., 2013). The AOB study, conducted in Calgary, Alberta, Canada, enrolled 3388 pregnant women (those participants who completed at least one survey) recruited from primary health care offices, community advertising, and the Calgary Laboratory Services. Self-reported questionnaires were administered at 17–24 weeks gestation and 34–36 weeks gestation, with response rates ranging from 76% to 84% (McDonald et al., 2013).

2.2. Participants

Inclusion criteria for eligible participants were; a minimum of 18 years old, ability to communicate in English, and receiving prenatal care in Calgary from August 2008 until July 2011. In Canada, 94.9% of women receive prenatal care within the first trimester of pregnancy (Public Health Agency of Canada, 2009). Pregnancies with multiple-gestation were excluded.

2.3. Measures of anxiety, depression and chronic stress

State anxiety was measured on the Speilberger State Anxiety Scale (Spielberger, 2010) to detect symptoms of anxiety and their magnitude (Julian, 2011). The scale is a self-report questionnaire including 20 questions on a 4-point Likert scale, with higher numbers corresponding to increasing anxiety (Spielberger, 2010). Scores range from 20 to 80, with a cutoff score of 40 and over indicating an anxious state (Lushene et al., 1970). Finally, the Cronbach's alpha is reported to be 0.89, indicating that the scale has high internal consistency (Barnes et al., 2002). Not only does the Spielberger State Anxiety Scale have high validity and reliability, but has also been validated and recommended for use in pregnant women, as it was shown to reflect anxiety-related experiences in this population (Gunning et al., 2010). These two factors were the basis for its selection in the AOB cohort study.

Depression was measured with the Edinburgh Postnatal Depression Scale (EPDS), which is a 10-item self-report screen that measures symptoms of depression during pregnancy (Cox et al., 1987). Each question can be assigned a score of 0, 1, 2, or 3; scores can range from 0 to 30, with higher numbers corresponding to worse depression (Cox et al., 1987). The EPDS has a Cronbach's alpha of 0.87, which is considered a reliable score (Knight et al., 1997). To classify whether someone had depressive symptoms, an established cutoff score of 10 or greater was used to indicate minor depression (Santos et al., 2007). An ROC curve analysis of various cut-off scores using the EPDS scale found that a cut-off score of 10 or greater had the best overall validity (Santos et al., 2007). Using this cut-off, the sensitivity was 82.7% (95% CI 74.0, 89.4) and the specificity was 65.3% (95% CI 59.4, 71.0).

Chronic stress was measured using the Perceived Stress Scale (PSS), which is often used as a proxy measure for chronic stress (Cohen et al., 1983). Chronic stress was assessed at one time point, at 17–24 weeks gestation. The PSS includes 10 items on a five-point Likert scale (range 0–40), where higher scores correspond to increased stress levels (Cohen et al., 1983). The questions prompt the participant to consider stressful

events, coping resources, and control over situations and emotions that have occurred over the past month. The PSS has a Cronbach's alpha and test-retest reliability of over 0.70 (both meeting the requirements of a minimal reliability) (Lee, 2012). Similar to a previous study using the same AOB dataset, those women with PSS scores in the 80th percentile were classified as having chronic stress (Raguz et al., 2014).

2.4. Covariates

A list of covariates was generated from key articles in the literature, as well as background knowledge of the topic. Potential modifiers included chronic stress, social support (measured using the Medical Outcomes Study Social Support Survey, with a cutoff score of 70 (Sherbourne and Stewart, 1991)), maternal age at delivery, ethnicity, having one or more previous PTB, and income. Potential confounders included parity, an increased volume of amniotic fluid (either diagnosed as polyhydramnios or oligohydramnios), smoking, or pregnancy complications (at least one of the following vaginal bleeding, placenta previa, placental abruption, preeclampsia, or gestational diabetes).

2.5. Analysis

Descriptive statistics were used to illustrate the demographic characteristics of the sample (Tables 1–3). Logistic regression was used to analyze the relationships between changes in anxiety, depression and PTB using hierarchically well-formulated models, which assessed modification by covariates, followed by an assessment of confounding by covariates. Separate regression models were used for anxiety and depression, in addition to a comprehensive model that assessed anxiety and depression together to understand how the variables interact with one another. PTB was classified as spontaneous PTB (with and without preterm premature rupture of membranes (PPROM)), and medically indicated PTB. Alternative definitions of PTB include spontaneous, medically indicated, and PPROM as a third classification (World Health Organization, 2015). However, spontaneous and PPROM PTB have similar gene expression profiles, and can be grouped together as a single classification (Heng et al., 2016). A multivariable logistic regression model was used to assess PTB as defined by two classifications, and a multinomial regression model was used to assess PTB as defined by three classifications. We used the mlogit command in STATA 13 to run the multinomial regression model, and used the option “rrr” to report relative-risk ratios.

To examine the relationship between changes in anxiety and depression during pregnancy and the risk of PTB, anxiety and depression were treated as continuous variables, as well as categorical variables with either two or four categories. Changes in scores were calculated by subtracting the scores obtained from the questionnaire administered in the third trimester from the score obtained in the second trimester. Clinically meaningful changes were calculated as a 10-point change for anxiety and a 3-point change for depression (Corsaletti et al., 2014; Matthey, 2004b). Anxiety and depression were assessed in three ways: as a variable with two categories, four categories, and as a continuous variable. When used as variables with two categories, anxiety and depression were categorized as either a clinically meaningful increase (an improvement of the condition) or a clinically meaningful decrease (a worsening of the condition). When anxiety and depression were used as

Table 1
Participant Sociodemographic Characteristics.

Covariate	Total Sample[a] n (%)	Full Term[a] n (%)	Preterm[a] n (%)
Maternal Age			
< 35 years	2184 (77.4)	2038 (77.3)	146 (79.8)
≥35 years	636 (22.6)	599 (22.7)	37 (20.2)
Ethnicity			
White/Caucasian	2220 (79.1)	2086 (79.4)	134 (74.9)
Other	585 (20.9)	540 (20.6)	45 (25.1)
Income			
High Income (≥$80 000)	1910 (70.2)	1799 (70.7)	111 (63.8)
Low Income (< $80 000)	810 (29.8)	747 (29.3)	63 (36.2)
School Education			
Completed High School or Less	294 (10.5)	275 (10.5)	19 (10.6)
Some or Completed Post-Secondary	2512 (89.5)	2351 (89.5)	161 (89.4)
Smoking			
No	2235 (88.4)	2108 (88.8)	127 (82.5)
Yes	293 (11.6)	266 (11.2)	27 (17.5)

[a] Due to missing data, sample numbers are not identical between groups.

Table 2
Participant psychosocial characteristics.

Covariate	Total Sample[a] n (%)	Full Term[a] n (%)	Preterm[a] n (%)
Anxiety			
Decreased (> =10 point change)	185 (7.7)	176 (7.8)	9 (6.5)
Increased (> =10 point change)	338 (14.1)	297 (13.1)	41 (29.7)
Consistently Low (score < 40)	1707 (71.0)	1636 (72.1)	71 (51.5)
Consistently High (score > =40)	176 (7.3)	159 (7.0)	17 (12.3)
Depression			
Decreased (> = 3 point change)	597 (22.5)	551 (22.1)	46 (28.6)
Increased (> =3 point change)	549 (20.7)	516 (20.7)	33 (20.5)
Consistently Low (score < 10)	1413 (53.2)	1340 (53.7)	73 (45.3)
Consistently High (score > =10)	98 (3.7)	89 (3.6)	9 (5.6)
Anxiety and Depression			
Both Decreased	113 (36.2)	108 (37.8)	5 (19.2)
Both Increased	199 (63.8)	178 (62.2)	21 (80.8)
Social Support (SS)			
High SS (score < 70)	2433 (87.2)	2284 (87.5)	149 (83.2)
Low SS (score ≥70)	357 (12.8)	327 (12.5)	30 (16.8)
Chronic Stress			
< 80th percentile (score < 19)	2215 (79.7)	2084 (80.1)	131 (74.0)
≥80th percentile (score ≥19)	564 (20.3)	518 (19.9)	46 (26.0)

[a] Due to missing data, sample numbers are not identical between groups.

Table 3
Participant obstetric characteristics.

Covariate	Total Sample[a] n (%)	Full Term[a] n (%)	Preterm[a] n (%)
Parity			
0 Previous Pregnancies	1377 (49.4)	1276 (48.8)	101 (57.4)
≥1 Previous Pregnancies	1412 (50.6)	1337 (51.2)	75 (42.6)
History of PTB			
No	2687 (95.3)	2533 (96.1)	154 (84.2)
Yes	132 (4.7)	103 (3.9)	29 (15.9)
Pregnancy Complications			
No	2290 (81.2)	2168 (82.2)	122 (66.7)
Yes (at least 1)	530 (18.8)	469 (17.8)	61 (33.3)
Polyhydramnios and/or Oligohydramnios			
No	2743 (97.3)	2577 (97.7)	166 (90.7)
Yes	77 (2.7)	60 (2.3)	17 (9.3)

[a] Due to missing data, sample numbers are not identical between groups.

variables with four categories, the categories included an increase in score, a decrease in score, consistently low levels of anxiety and depression, and consistently high levels. In order to be classified as having "consistently low" or "consistently high" anxiety or depression, a change of score of < 10 for anxiety and < 3 for depression were required. For assessing co-occurring changes in depression and anxiety, there was not enough power to analyze as four categorical outcomes, so the analysis only compared two categories: a clinically meaningful increase in both anxiety and depression, to a clinically meaningful decrease in both anxiety and depression.

In order to assess important covariates in this analysis, a bivariate analysis was conducted on potential confounders to ensure that they were associated with both the exposures (anxiety or depression) and the outcome (PTB). Variables were excluded from the analysis if they were not significantly associated with either the outcome or exposures (using an alpha significance level of 0.1). To assess chronic stress as a potential modifier, women who were identified as having chronic stress at 17–24 weeks' gestation were compared to those who were not identified as having chronic stress. Chronic stress and other covariates were first assessed as potential modifiers in the analysis. This was accomplished by creating interaction terms between modifiers and each variable of interest. An omnibus likelihood ratio test was then used to identify whether any modification was present in the model, with the significance level set to a p-value of < 0.05. If the covariates were not modifiers, they were assessed as potential confounding variables. A covariate was considered a confounder if the adjusted odds ratio (aOR) was different from the crude odds ratio (OR).

3. Results

3.1. Participant characteristics

The overall rate of PTB was 6.4% in the AOB dataset (n = 183/2858). Participants' sociodemographic, psychosocial, and obstetric characteristics are described in Tables 1–3 (respectively). Some women experienced low levels of social support (12.8%), and 20.3% of women experienced chronic stress. When examining changes in anxiety between the two time points,14.1% of women experienced an increase in anxiety score, while 7.3% had consistently high anxiety scores. When examining changes in depression, 20.7% of women had an increase in depression score, while 3.7% had consistently high depression scores.

3.2. Modification by chronic stress and other covariates

Chronic stress, social support, maternal age at delivery, ethnicity, having a history of PTB, and income did not significantly modify any of the relationships between changes in anxiety and depression, and PTB. Chronic stress was not found to modify the relationship between A) changes in anxiety (Table 4); B) changes in depression (Table 5); C) co-occurring worsening of both anxiety and depression (Table 6); D) changes in anxiety and the two classifications of PTB (Table 6), and E) changes in depression and the three causes of PTB (Table 7, Supplementary file).

All of the presented regression models (presented in Tables 4–7) accounted for covariates that were found to be potential confounding variables: parity, an increased volume of amniotic fluid, smoking, pregnancy complications, chronic stress, social support, maternal age at delivery, ethnicity, having a history of PTB, and income. However, the odds ratios in each of the multivariable models were similar to the odds ratios in the crude models, indicating that there was negligible confounding present in the models. Therefore, as there was neither modification nor confounding in each of the models, the crude model is used to report the final measure of association, although both are presented.

3.3. The change in anxiety and PTB

Women who showed an increase in anxiety scores between the second and third trimesters had significantly greater odds of delivering preterm (n = 41/338 (12%)) compared to those women who had a decline (n = 9/185 (5%)) in anxiety scores (OR = 2.70, 95% CI 1.28, 5.69; p = 0.009) (Table 4.). Women who had consistently low anxiety (71/1707 (4%)) did not have significantly greater odds of delivering preterm compared to those with a decline (n = 9/185 (5%)) in anxiety scores (OR = 0.85, 95% CI 0.42, 1.73; p = 0.651). Consistently anxious women (17/176 (10%)) were also not at significantly greater odds of delivering preterm (OR = 2.09, 95% CI 0.91, 4.82; p = 0.084). When measuring anxiety as a continuous variable, for every decrease of one point on the anxiety scale, women had 4% lower odds of delivering preterm infants (OR = 0.96, 95% CI 0.94, 0.98; p = 0.001).

3.4. The change in depression and PTB

Unlike anxiety, there was no relationship between an increase in depression scores (n = 33/549 (6%)) and PTB, compared to a decline (n = 46/597 (8%)) in depression scores (OR = 0.77, 95% CI 0.48, 1.22; p = 0.259). Those women that had consistently low depression (73/1413 (5%)) had reduced odds of delivering preterm, compared to those women that had a decreased depression score at two time points (OR 0.65, 95% CI 0.45, 0.96; p = 0.029). However, the effect was attenuated and no longer significant after including the covariates in the model (aOR = 0.72, 95% CI 0.45, 1.14; p = 0.159). These results are shown in Table 5.

3.5. Co-occurring changes in anxiety and depression, and PTB

Due to sample size limitations, the analysis of co-occurring changes in anxiety and depression did not include consistently low or consistently high anxiety and depression. In the first instance, the variables were treated as categorical variables. The odds of PTB in those who had a worsening of both anxiety and depression between the second and third trimesters of pregnancy (21/199, 10.6%) were compared to the odds of PTB in women who delivered preterm with an improvement in both anxiety and depression (5/113, 4.4%). There was not a significant relationship between co-occurring worsening of anxiety and depression, and PTB (OR = 2.55, 95% CI 0.93, 6.96; p = 0.068). In the second instance, a simultaneous increase in anxiety and depression scores was

Table 4
Change in Anxiety and PTB.

Model	Modification? (P-Value LR Test)	Crude OR (95% CI)	P-Value	Adjusted OR[a] (95% CI)	P-Value
Anxiety: Decrease (baseline) vs Increase	No (0.325)	**2.70 (1.28, 5.69)**	**0.009**	**2.35 (1.01, 5.45)**	**0.048**[a]
Anxiety: Decrease (baseline) vs	No (0.460)	**1: 2.70 (1.28, 5.69)**	**0.009**	**1: 2.82 (1.24, 6.44)**	**0.014**[a]
1. Increase,		2: 0.85 (0.42, 1.73)	0.651	2: 0.97 (0.44, 2.17)	0.949
2. Consistently Low,		3: 2.09 (0.91, 4.82)	0.084	3: 2.09 (0.84, 5.24)	0.114
3. Consistently High					
Δ Anxiety Score	No (0.815)	**0.96 (0.94, 0.98)**	**< 0.001**	**0.96 (0.94, 0.98)**	**0.001**[a]

[a] Multivariable models accounted for the following confounding variables: parity, an increased volume of amniotic fluid, smoking, pregnancy complications, chronic stress, social support, maternal age at delivery, ethnicity, having a history of PTB, and income.

Table 5
Change in Depression and PTB.

Model	Modification? (P-Value LR Test)	Crude OR (95% CI)	P-Value	Adjusted OR[a] (95% CI)	P-Value
Depression: Decrease (baseline) vs Increase	No (0.604)	0.77 (0.48, 1.22)	0.259	0.92 (0.53, 1.59)	0.763
Depression: Decrease (baseline) vs:	No (0.278)	1: 0.77 (0.48, 1.22)	0.259	1: 0.86 (0.51, 1.46)	0.584
1. Increase,		**2: 0.65 (0.45, 0.96)**[a]	**0.029**	2: 0.72 (0.45, 1.14)	0.159
2. Consistently Low,		3: 1.21 (0.57, 2.56)	0.616	3: 1.59 (0.70, 3.63)	0.271
3. Consistently High					
Δ Depression Score	No (0.534)	1.01 (0.97, 1.06)	0.542	1.00 (0.96, 1.05)	0.984

[a] Multivariable models accounted for the following confounding variables: parity, an increased volume of amniotic fluid, smoking, pregnancy complications, chronic stress, social support, maternal age at delivery, ethnicity, having a history of PTB, and income.

assessed (i.e. as continuous variables). The crude model also did not show significant associations between improved anxiety and depression, and PTB (OR = 1.00, 95% CI 1.00, 1.01; p = 0.083).

3.6. Analysis of PTB classifications

As shown in Table 6, a classic logistic regression model was used to assess the relationship between changes in anxiety and depression, and PTB defined as two separate categories: medically indicated and spontaneous birth. Depression and anxiety were assessed as continuous variables, and not as categorical variables, due to sample size limitations; as such, the odds ratios quantify the effect of a change of score of one on the scale. An improvement in depression during pregnancy did not appear to significantly influence the odds of delivering either spontaneous or medically indicated PTB. However, age modified the relationship between changes in anxiety and PTB. Those women 35 years of age and over had greater odds of having a medically indicated preterm birth rather than a spontaneous preterm birth, with the odds increasing by about 9% with change of one point on the scale. Women under 35 did not have greater odds of delivering preterm due to either of the classifications.

4. Discussion

Women who experience an escalation in anxiety symptoms during pregnancy are at greater odds of delivering preterm compared to those who experience an improvement in anxiety. Our finding is consistent with previous research, which demonstrated a significant association between increasing anxiety scores during pregnancy and PTB (Bayrampour, McDonald and Tough, 2015; Glynn et al., 2008). Anxiety is suggested to increase the risk of PTB by increasing hypothalamic-pituitary-adrenocortical (HPA) axis activity (Obel et al., 2005). Because typical pregnancies exhibit a decline in anxiety, this increase in anxiety is a marked departure from normal physiological responses (Glynn et al., 2004). One group of investigators demonstrated that corticotropin-releasing hormone (CRH), which is released when anxiety stimulates the HPA axis, was significantly higher in women who delivered preterm infants compared to those who delivered full term infants (Mancuso et al., 2004). These studies provide a possible physiological explanation of how increasing maternal anxiety during pregnancy can lead to PTB. Consistently high anxiety was not associated with increased odds of PTB. This may be due to lack of power to detect the effect, and that consistently high anxiety may still cause harm during pregnancy.

The AOB cohort study did not measure pregnancy-specific anxiety, which was found in one study to be a stronger predictor of PTB compared to other forms of anxiety (Staneva et al., 2015). Another contrasting systematic review and meta-analysis, after controlling for heterogeneity, revealed that the odds of delivering preterm when exposed to pregnancy-specific anxiety compared to state anxiety were not different (OR 1.67, 95% CI 1.35, 2.07; OR 1.70, 95% CI 1.33, 2.18, respectively) (Rose et al., 2016). These authors suggested that these two unique constructs of anxiety have potentially similar implications for the HPA axis response and allostatic load, that may lead to PTB (Rose et al., 2016). Rose et al. did not discuss the interaction between pregnancy-specific anxiety and state anxiety. Not only is it important to clarify the relationship between changes in state anxiety and PTB, but also future studies should examine how state anxiety can interact with pregnancy-specific anxiety, and possibly elevate the risk for PTB.

Unlike anxiety, an increase in depression scores during pregnancy did not significantly increase the odds of PTB. However, women who had consistently low depression had reduced odds of delivering preterm compared to women who had reduced depression scores during pregnancy. These results indicate that consistently low depression levels appear protective from PTB, however this effect became insignificant in the model that adjusted for potential covariates. There is a possibility that the significant results of the crude analysis are due to a type I error. Only 73 women had consistently low depression, and only 46 women had reduced depressive symptoms. In addition, depression may increase the risk of PTB through poor behavioral outcomes such as substance abuse, low social support, and smoking (Kelly et al., 2002; Zuckerman et al., 1989). The sample in the current study was affluent with a low prevalence of smoking (11.6%) and a high prevalence of high social support (87.2%) (McDonald et al., 2013b). These results should be interpreted within the context of the urban Canadian parenting population where this sample was slightly more affluent.

A simultaneous worsening of anxiety and depression during pregnancy was not found to have an effect on PTB. This is contradictory to the literature, as comorbid depression and anxiety during pregnancy increased the risk of PTB in a prospective cohort study with a sample size of 911 participants (Field et al., 2010). However, small sample numbers limited the analysis of the current study. Only 5 women who delivered preterm had a simultaneous worsening of both anxiety and depression, and only 21 women had a simultaneous improvement in

Table 6
Anxiety and depression and two classifications of PTB.

Model	Modification? (P-Value LR Test)	Crude OR (95% CI)	P-Value	Adjusted OR[a] (95% CI)	P-Value
Δ Anxiety Scores:	Yes	1.03 (0.99, 1.07)	0.154	Age < 35: 1.04 (0.99, 1.09)	0.093
Medically Indicated/Spontaneous	(p = 0.0229)			**Age ≥35: 1.09 (1.02, 1.16)**	**0.009**
Δ Depression Scores:	No	1.06 (0.97, 1.16)	0.176	1.11 (0.98, 1.25)	0.089
Medically Indicated/Spontaneous	(p = 0.7435)				

[a] Multivariable models accounted for the following confounding variables: parity, an increased volume of amniotic fluid, smoking, pregnancy complications, chronic stress, social support, maternal age at delivery, ethnicity, having a history of PTB, and income.

Table 7
Anxiety and depression and three classifications of PTB.

Model[b]	Modification? (P-Value LR Test)	Crude RR (95% CI)	P-Value	Adjusted RR[a] (95% CI)	P-Value
Δ Anxiety Scores	No (p = 0.093)	PPROM/Spontaneous: 0.97 (0.92, 1.03)	0.359	PPROM/Spontaneous: 0.94 (0.87, 1.01)	0.114
		Medically Indicated/Spontaneous: 1.02 (0.98, 1.06)	0.255	Medically Indicated/Spontaneous: 1.04 (0.98, 1.09)	0.170
Δ Depression Scores	No (p = 0.732)	PPROM/Spontaneous: 0.91 (0.79, 1.05)	0.195	PPROM/Spontaneous: 0.86 (0.72, 1.03)	0.102
		Medically Indicated/Spontaneous: 1.04 (0.96, 1.14)	0.341	Medically Indicated/Spontaneous: 1.09 (0.96, 1.22)	0.185

[a] Multivariable models accounted for the following confounding variables: parity, an increased volume of amniotic fluid, smoking, pregnancy complications, chronic stress, social support, maternal age at delivery, ethnicity, having a history of PTB, and income.
[b] Multinomial regression models, which use risk ratios as a measure of association, were used to assess whether changes in anxiety or depression would be associated with the three classifications of PTB.

anxiety and depression. Similarly, changes in depression did not impact the risk of delivering a spontaneous or medically indicated PTB differently. However, women who were 35 years of age and over with increases in anxiety scores had greater odds of having a medically indicated PTB, compared to a spontaneous PTB. Women who were under 35 years of age with increases in anxiety scores were not statistically more likely to have a medically indicated PTB; this finding is supported in the literature (Henderson et al., 2012). The literature has shown that allostatic load accumulates with age, posing greater health risks to women as they age (Chyu and Upchurch, 2011). This may help explain why older women are more susceptible to medically indicated PTB. Future interventions should target this group of women, and intervene early on in pregnancy to reduce the risk of delivering preterm.

Chronic stress and other important potential modifiers (i.e. social support, maternal age, ethnicity, history of PTB, and income) were not found to significantly influence any of the relationships assessed in the current study. One possible reason why chronic stress was not a modifier is that the number of pregnant women who experienced chronic stress was small (20.3%), thus limiting the ability to detect the effect of chronic stress on the relationship between changes in anxiety and depression, and PTB. Additionally, the analysis of chronic stress as a modifier may also be limited as a result of low power. Participants in the AOB cohort were more affluent than the target population, thus chronic stress was likely lower in this sample and may explain the negative results (McDonald et al., 2013). Although the PSS has been used as a measure for chronic stress, it is recommended that the instrument be administered multiple times to get a true sense of the ongoing "chronic" stress that pregnant women might be experiencing (Cohen et al., 1983). However, chronic stress does not have a defined beginning or end point (Dunkel Schetter and Dolbier, 2011). Future clarification around the definition of chronic stress, and implementing the PSS scale at multiple time points before and during pregnancy, will help more critically examine the influence of chronic stress on PTB and its potential role in modifying the association between changes in anxiety and depression, and PTB.

This study is not without its limitations. The sample size did not allow the analysis of how changes in anxiety and depression during pregnancy influence the three severities of PTB (extremely preterm, early preterm, and late preterm), as extremely preterm and early preterm infants represent less than 16% of all births, and consequently numbers are small in the AOB dataset (Blencowe et al., 2012). Further, the current study found that some estimates had wide confidence intervals, indicating imprecision of the estimates. Increasing the sample size may help alleviate this issue. Future studies will need to increase the number of women who delivered preterm, in order to comprehensively assess these relationships. This study was also not able to examine changes in anxiety and depression earlier than in the 2nd trimester of pregnancy. The majority of preterm infants are late preterm, and therefore different strategies may be necessary to understand the relationship between anxiety and depression on infants of very early gestational ages.

Anxiety was assessed using the Spielberger State Anxiety Scale, which asks respondents to consider how they are feeling in that moment when responding to each item (Spielberger, 2010). Because the AOB cohort study mailed out the questionnaires to participants, they did not control for the environment or time that the questionnaire was filled out. Our study also only assessed state anxiety, but it would be informative to assess other types of anxiety such as pregnancy-related anxiety (e.g., pregnancy-specific anxiety), as well assess anxiety using other methodologies (e.g., qualitative interviews). When categorizing women as having a clinically meaningful increase or decrease in anxiety or depression scores, women with lower scores will have been grouped with women with higher scores (e.g., a woman with an increase in anxiety from 8 to 19 will be grouped with a woman with an increase from 38 to 49). This may be grouping together women with different mental health characteristics. Although this study aimed to look at how the change in anxiety and depression would be associated with PTB, it would be critical for future studies to separate out these groups of women. Further, categorization of ordinal measures using cut-points may lead to a loss of some information, but also helps to link the results to interpretive thresholds that are viewed as being clinically meaningful. For example, cut-points of 13 and 15 for the EPDS have also been used for Research Diagnostic Criteria major depression and the Diagnostic and Statistical Manual of Mental Disorders major depression, respectively (Murray and Cox, 1990). Clinically meaningful changes on the EPDS and Spielberger State Anxiety Scale also vary across the literature, where some studies have reported using a change of 4 points as a clinically meaningful change using the EPDS (Matthey, 2004a). Future studies should seek to replicate these findings using clinically defined categories (e.g., specific diagnoses) and also explore anxiety levels without application of cut-points. Finally, there remains a possibility that some important covariates were not considered in the analysis.

The current research provides necessary information to develop a future prospective longitudinal study, which can confirm the current findings and re-examine the relationships that this study was not able to explore (e.g. how increases in anxiety during pregnancy influences the risk of delivering extremely preterm, very preterm, or late preterm). This future study would ideally use gold standard measures of chronic stress. Additionally, it would explore the potential interactive effects of anxiety, depression and chronic stress. This future prospective longitudinal study can additionally assess biological plausibility by measuring the expression of markers of PTB, and measure anxiety and depression at multiple points in pregnancy. The ultimate goal of this research will be to help decision-makers implement a primary prevention initiative, such as reducing levels of prenatal anxiety through implementation of stress reduction workshops. Such an initiative would ultimately reduce the risk of PTB in at-risk women.

Compliance with ethical standards

This research was conducted in accordance with prevailing ethical principles and was approved by the Conjoint Health Research Ethics Board. An amendment to the AOB cohort study ethics agreement was made to incorporate the first author as a researcher on the project (ethics ID: REB15-0248_MOD1). Because we are performing secondary data analysis on existing de-identified questionnaires, all necessary data privacy precautions were implemented.

Author disclosure

Contributors

Chelsea Doktorchik helped formulate the research questions, analyzed and interpreted the data, and drafted the manuscript; Shahirose Premji helped formulate the research questions, and supervised the data analysis and interpretation; Donna Slater helped formulate the research question, and provided guidance on the interpretation of the results and the drafting of the manuscript; Tyler Williamson supervised the analysis and interpretation of the data, and provided guidance on the drafting of the manuscript; Suzanne Tough provided content expertise on the dataset, and assisted with the ethics process and formation of the research questions; and Scott Patten helped design the study, supervised the interpretation of the data analysis, and provided guidance on the drafting of the manuscript. All authors contributed to, read and approved the final manuscript.

Role of the funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We would like to thank Ms. Nikki Stephenson and the AOB research team for their support and guidance with the dataset and analysis.

Conflict of interest

The authors have no competing interests to declare.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2017.10.001.

References

Accortt, E.E., Cheadle, A.C., Dunkel Schetter, C., 2015. Prenatal depression and adverse birth outcomes: an updated systematic review. Matern. Child Health J. 19, 1306–1337.

Barnes, L.L.B., Harp, D., Jung, W.S., 2002. Reliability generalization of scores on the spielberger state-trait anxiety inventory. Educ. Psychol. Meas. 62, 603–618.

Bayrampour, H., McDonald, S., Tough, S., 2015. Risk factors of transient and persistent anxiety during pregnancy. Midwifery 31, 582–589.

Blencowe, H., Cousens, S., Oestergaard, M.Z., Chou, D., Moller, A.B., Narwal, R., ... Lawn, J.E., 2012. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 379, 2162–2172.

Brandon, D.H., Tully, K.P., Silva, S.G., Malcolm, W.F., Murtha, A.P., Turner, B.S., Holditch-Davis, D., 2011. Emotional responses of mothers of late-preterm and term infants. J. Obstet. Gynecol. Neonatal. Nurs. 40, 719–731.

Canadian Institute for Health Information, 2016. QuickStats: Childbirth indicators by place of residence. Preterm birth rate, Alberta. 〈https://apps.cihi.ca/mstrapp/asp/Main.aspx?Evt=2048001&documentID=029DB170438205AEBCC75B8673CCE822&Server=apmstrextprd_i&Project=Quick+Stats&〉 (Accessed 1 August 2016).

Chrousos, G.P., 1998. Stressors, stress, and neuroendocrine integration of the adaptive response: the 1997 Hans Selye Memorial Lecture. Ann. N. Y. Acad. Sci. 851, 311–335.

Chyu, L., Upchurch, D.M., 2011. Racial and ethnic patterns of allostatic load among adult women in the United States: findings from the National Health and Nutrition Examination Survey 1999–2004. J. Women Health 20, 575–583.

Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. J. Health Soc. Behav. 24, 385–396.

Corsaletti, B.F., Proença, M.-D.G.L., Bisca, G.K.W., Leite, J.C., Bellinetti, L.M., Pitta, F., 2014. Minimal important difference for anxiety and depression surveys after intervention to increase daily physical activity in smokers. Fisioter. Pesqui. 21, 359–364.

Cox, J.L., Holden, J.M., Sagovsky, R., 1987. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. Br. J. Psychiatry 150, 782–786.

Dayan, J., Creveuil, C., Marks, M.N., Conroy, S., Herlicoviez, M., Dreyfus, M., Tordjman, S., 2006. Prenatal depression, prenatal anxiety, and spontaneous preterm birth: a prospective cohort study among women with early and regular care. Psychosom. Med. 68, 938–946.

Ding, X.X., Wu, Y.L., Xu, S.J., Zhu, R.P., Jia, X.M., Zhang, S.F., Huang, K., Zhu, P., Hao, J.H., Tao, F.B., 2014. Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. J. Affect. Disord. 159, 103–110.

Dunkel Schetter, C., Dolbier, C., 2011. Resilience in the context of chronic stress and health in adults. Soc. Personal. Psychol. Compass 5, 634–652.

Dunkel Schetter, C., Tanner, L., 2012. Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice. Curr. Opin. Psychiatry 25, 141–148.

Field, T., Diego, M., Hernandez-Reif, M., Figueiredo, B., Deeds, O., Ascencio, A., Schanberg, S., Kuhn, C., 2010. Comorbid depression and anxiety effects on pregnancy and neonatal outcome. Infant Behav. Dev. 33, 23–29.

Glynn, L., Wadhwa, P., Dunkel-Schetter, C., Chicz-Demet, A., Sandman, C., 2001. When stress happens matters: effects of earthquake timing on stress responsivity in pregnancy. Am. J. Obstet. Gynecol. 184, 637–642.

Glynn, L.M., Schetter, C.D., Wadhwa, P.D., Sandman, C.A., 2004. Pregnancy affects appraisal of negative life events. J. Psychosom. Res. 56, 47–52.

Glynn, L.M., Schetter, C.D., Hobel, C.J., Sandman, C.A., 2008. Pattern of perceived stress and anxiety in pregnancy predicts preterm birth. Health Psychol. 27, 43–51.

Gunning, M.D., Denison, F.C., Stockley, C.J., Ho, S.P., Sandhu, H.K., Reynolds, R.M., 2010. Assessing maternal anxiety in pregnancy with the State-Trait Anxiety Inventory (STAI): issues of validity, location and participation. J. Reprod. Infant Psychol. 28, 266–273.

Henderson, J.J., McWilliam, O.A., Newnham, J.P., Pennell, C.E., 2012. Preterm birth aetiology 2004–2008. maternal factors associated with three phenotypes: spontaneous preterm labour, preterm pre-labour rupture of membranes and medically indicated preterm birth. J. Matern.-Fetal Neonatal Med. 25, 642–647.

Heng, Y.J., Pennell, C.E., McDonald, S.W., Vinturache, A.E., Xu, J., Lee, M.W.F., Briollais, L., Lyon, A.W., Slater, D.M., Bocking, A.D., 2016. Maternal whole blood gene expression at 18 and 28 weeks of gestation associated with spontaneous preterm birth in asymptomatic women. PloS One 11, e0155191.

Institute of Medicine Committee, 2007. The national academies collection: reports funded by National Institutes of Health. In: Behrman, R.E., Butler, A.S. (Eds.), Preterm birth: Causes, Consequences, and Prevention. National Academies Press (US) National Academy of Sciences., Washington, DC).

Johnston, K.M., Gooch, K., Korol, E., Vo, P., Eyawo, O., Bradt, P., Levy, A., 2014. The economic burden of prematurity in Canada. BMC Pediatr. 14, 93.

Julian, L.J., 2011. Measures of anxiety: state-trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and hospital Anxiety and depression scale-Anxiety (HADS-A). Arthritis Care Res. 63 (Suppl 11), S467–S472.

Kelly, R.H., Russo, J., Holt, V.L., Danielsen, B.H., Zatzick, D.F., Walker, E., Katon, W., 2002. Psychiatric and substance use disorders as risk factors for low birth weight and preterm delivery. Obstet. Gynecol. 100, 297–304.

Knight, R.G., Williams, S., McGee, R., Olaman, S., 1997. Psychometric properties of the centre for Epidemiologic studies depression scale (CES-D) in a sample of women in middle life. Behav. Res. Ther. 35, 373–380.

Latendresse, G., 2009. The interaction between chronic stress and pregnancy: preterm birth from a biobehavioral perspective. J. Midwifery Women Health 54, 8–17.

Lee, E.H., 2012. Review of the psychometric evidence of the perceived stress scale. Asian Nurs. Res. 6, 121–127.

Lushene, R.E., Gorsuch, R.L., Spielberger, C.D., 1970. Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, CA.

Mancuso, R.A., Schetter, C.D., Rini, C.M., Roesch, S.C., Hobel, C.J., 2004. Maternal prenatal anxiety and corticotropin-releasing hormone associated with timing of delivery. Psychosom. Med. 66, 762–769.

Matthey, S., 2004a. Calculating clinically significant change in postnatal depression studies using the Edinburgh Postnatal Depression Scale. J. Affect. Disord. 78, 269–272.

Matthey, S., 2004b. Detection and treatment of postnatal depression (perinatal depression or anxiety). Curr. Opin. Psychiatry 17, 21–29.

McDonald, S.W., Lyon, A.W., Benzies, K.M., McNeil, D.A., Lye, S.J., Dolan, S.M., Pennell, C.E., Bocking, A.D., Tough, S.C., 2013. The All Our Babies pregnancy cohort: design, methods, and participant characteristics. BMC Pregnancy Childbirth 13 (Suppl 1), S2.

McEwen, B.S., Seeman, T., 1999. Protective and damaging effects of mediators of stress: elaborating and testing the concepts of allostasis and allostatic load. Ann. N. Y. Acad. Sci. 896, 30–47.

Murray, D., Cox, J.L., 1990. Screening for depression during pregnancy with the Edinburgh Depression Scale (EDDS). J. Reprod. Infant Psychol. 8, 99–107.

Obel, C., Hedegaard, M., Henriksen, T.B., Secher, N.J., Olsen, J., Levine, S., 2005. Stress and salivary cortisol during pregnancy. Psychoneuroendocrinology 30, 647–656.

Public Health Agency of Canada, 2009. What Mothers Say: The Canadian Maternity Experiences Survey, Ottawa. 〈http://www.phac-aspc.gc.ca/rhs-ssg/survey-eng.php〉

(Accessed 1 October 2016).
Public Health Agency of Canada, 2013. Perinatal health indicators for Canada 2013: A report from the Canadian perinatal surveillance system. 〈http://www.phac-aspc.gc.ca/rhs-ssg/phi-isp-2013-eng.php〉 (Accessed 1 October 2016).
Raguz, N., McDonald, S.W., Metcalfe, A., O'Quinn, C., Tough, S.C., 2014. Mental health outcomes of mothers who conceived using fertility treatment. Reprod. Health 11, 19.
Rose, M.S., Pana, G., Premji, S., 2016. Prenatal maternal anxiety as a risk factor for preterm birth and the effects of heterogeneity on this relationship: a systematic review and meta-analysis. BioMed. Res. Int. 8312158.
Santos, I.S., Matijasevich, A., Tavares, B.F., Barros, A.J.D., Botelho, I.P., Lapolli, C., Magalhães, P.Vd.S., Barbosa, A.P.P.N., Barros, F.C., 2007. Validation of the Edinburgh postnatal depression scale (EPDS) in a sample of mothers from the 2004 Pelotas birth cohort study. Cad. Saúde Pública 23, 2577–2588.
Sherbourne, C.D., Stewart, A.L., 1991. The MOS social support survey. Soc. Sci. Med. 32, 705–714.
Spielberger, C.D., 2010. State-Trait Anxiety Inventory. John Wiley & Sons, Inc, Hoboken, New Jersey.
Staneva, A., Bogossian, F., Pritchard, M., Wittkowski, A., 2015. The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: a systematic review. Women Birth 28, 179–193.
Stoll, B.J., Hansen, N.I., Bell, E.F., Shankaran, S., Laptook, A.R., Walsh, M.C., Hale, E.C., Newman, N.S., Schibler, K., Carlo, W.A., 2010. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. Pediatrics 126, 443–456.
Vigod, S.N., Villegas, L., Dennis, C.L., Ross, L.E., 2010. Prevalence and risk factors for postpartum depression among women with preterm and low-birth-weight infants: a systematic review. BJOG: Int. J. Obstet. Gynaecol. 117, 540–550.
World Health Organization, 2012. Born too soon: The global action report on preterm birth. 〈http://www.who.int/pmnch/media/news/2012/preterm_birth_report/en/〉 (Accessed 1 July 2016).
World Health Organization, 2015. Preterm Birth. 〈http://www.who.int/mediacentre/factsheets/fs363/en/〉 (Accessed 1 July 2016).
Zuckerman, B., Amaro, H., Bauchner, H., Cabral, H., 1989. Depressive symptoms during pregnancy: relationship to poor health behaviors. Am. J. Obstet. Gynecol. 160, 1107–1111.