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Depression, Anxiety and Stress among Pregnant Migraineurs in a Pacific-Northwest Cohort

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Abstract

Background—The co-occurrence of migraine and unipolar psychiatric disorders has been well documented in non-pregnant populations, however little is known in pregnant populations.

Methods—A cohort of 1,321 women was interviewed during the first trimester of pregnancy. At the time of interview lifetime migraine status was ascertained using International Classification of Headache Disorders diagnostic criteria (ICHD-II). Information regarding unipolar depression, anxiety and stress during pregnancy was collected using the Patient Health Questionnaire Depression Module-9 (PHQ-9), and the Depression Anxiety Stress Scales 21-item Short Form (DASS-21). Multivariable logistic regression procedures were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association of migraine and mood disorders during pregnancy.

Results—Approximately 28.2% (N=372) were classified as having a lifetime history of migraine; among migraineurs 122 were classified as migraineurs with aura and 250 as migraineurs without aura. Compared with non-migraineurs, migraineurs were associated with 1.60-fold increased odds of depression as measured by a PHQ-9 score ≥10 (AOR=1.60; 95% CI: 1.12–2.31). Overall, migraine with aura was more strongly associated with depression than was migraine without aura. Migraineurs, as compared with non-migraineurs, also had higher odds of mood disorders as measured by the DASS-21.

Conclusions—The comorbidity of mood and migraine disorders in pregnant populations supports the need for integrated mental and physical clinical evaluation, increased vigilance, and treatment of patients with such disorders.

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Keywords

Migraine; Pregnancy; Depression; Stress; Anxiety

Introduction

Headache disorders, the most prevalent disorders of the neurological system, disproportionately affect women of reproductive age (Buse et al., 2013; Smitherman et al., 2013; WHO, 2011). Despite their non-lethality, migraines are a personal and societal burden, ubiquitous, and disabling (WHO, 2011). Estimates of lifetime prevalence of migraine among pregnant women range from 9–20% (Adeney et al., 2006; Frederick et al., 2014). Several studies have reported higher frequencies of preterm delivery, low birth weight, placental abruption, preeclampsia, and other hypertensive disorders among pregnant migraineurs when compared to pregnant non-migraineurs (Adeney and Williams, 2006; Chen et al., 2010; Marozio et al., 2012; Sanchez et al., 2010; Williams et al., 2011).

Mood and anxiety disorders are complications during pregnancy and the postpartum period (O'Hara and Wisner, 2014). Meta-analyses of perinatal depression report point prevalence estimates between 6–13% (Gavin et al., 2005) and studies have shown that 16% present with clinically anxious symptoms during the first trimester (Rubertsson et al., 2014); in addition, 84% of women report some form of psychosocial stress during pregnancy (Woods et al., 2010). Depression, anxiety, and stress during pregnancy have been associated with inadequate antenatal care, low birth weight, preterm delivery, small gestational age, placental abruption, self-harm, suicidal-ideation, postpartum depression, and maladaptive emotional and behavioral development of offspring (de Paz et al., 2011; Farias et al., 2013; Graignic-Philippe et al., 2014; Lee et al., 2007; Sanchez et al., 2013; Satyanarayana et al., 2011; Szegda et al., 2014; Wisner et al., 2013).

The World Health Organization (WHO) estimates that depression is three times more common in people with migraine or severe headaches compared to healthy individuals (WHO, 2012). The co-occurrence of migraine and mood disorders has been well documented in non-pregnant populations (Breslau et al., 1994; Breslau et al., 2003; Fuller-Thomson et al., 2013; Gelaye et al., 2013; Jette et al., 2008; Kalaydjian and Merikangas, 2008; McWilliams et al., 2004; Merikangas et al., 1990; Nguyen and Low, 2013; Patel et al., 2004; Saunders et al., 2014; Swartz et al., 2000; Zwart et al., 2003). Recent evidence suggests that migraine and mood disorders may be common among pregnant women (Cripe et al., 2010; Williams et al., 2010). In a study of 2,293 pregnant women, 55.1% of migraineurs reported moderate to severe depressive symptoms during pregnancy compared to 36.7% of pregnant non-migraineurs (Cripe et al., 2010). Furthermore, migraineurs score higher on the Perceived Stress Scale (PSS) than non-migraineurs during the first trimester of pregnancy (mean ± SD: 4.2 ± 2.4 vs. 3.7 ± 2.3; p-value: 0.008) (Williams et al., 2010). To our knowledge very few studies have reported on the co-occurrence of migraine and mood disorders during the antepartum period (Cripe et al., 2011; Cripe et al., 2010; Williams et al., 2010). Therefore, we sought to examine the extent to which migraine is associated with

depression, anxiety, and stress during pregnancy from a large prospective cohort study of pregnant women.

METHODS

2.1 Study population and Data Collection Procedures

This study was conducted among 1,321 pregnant women enrolled in the ongoing Migraine and Pregnancy Study, a prospective cohort study designed to investigate the relationship between migraine and headache symptoms prior to and during pregnancy, and the risk of adverse perinatal outcomes including preeclampsia. Pregnant women attending prenatal care at clinics affiliated with the Swedish Medical Center in Seattle Washington from November 2009 to March 2013 were recruited. Women were eligible if they initiated prenatal care at or prior to 20 weeks gestation, were 18 years of age or older, spoke and read English, planned to carry the pregnancy to term, and planned to deliver at the Swedish Medical Center. At enrollment participants completed an interviewer-administered survey where information regarding sociodemographics, pre-pregnancy general health, reproductive and medical history, and migraineur status were collected. Participants were then asked to complete two brief self-administered survey instruments to screen for symptoms of depression, anxiety, and stress using the Patient Health Questionnaire Depression Module-9 (PHQ-9), and the Depression Anxiety Stress Scales 21-item Short Form (DASS-21), both of which have been validated for use in perinatal populations (Kroenke et al., 2001; Meades and Ayers, 2011; Spitzer et al., 2000; Zhong et al., 2014). Multiple psychiatric instruments were used to improve our ability to assess maternal antepartum mood disorders as they relate to migraine status. The procedures used in the study were in agreement with the protocol approved by the Institutional Review Board of Swedish Medical Center, Seattle, WA. All participants provided written informed consent.

2.2 Survey Instruments

Migraine—Migraine was assessed using a structured questionnaire adapted from the deCode Genetics migraine questionnaire (DMQ3). The DMQ3 was recently validated to diagnose migraine with a sensitivity of 99%, specificity of 86%, and kappa statistic of 0.89 (Kirchmann et al., 2006). During the migraine assessment participants were asked if they had ever experienced headache episodes. Headache classification was determined using the International Classification of Headache Disorders diagnostic criteria (ICHD-II), established by the International Headache Society (ICHD, 2004). Women with “any migraine” refer to women with definitive migraine. Definitive migraine was defined by at least 5 lifetime headache attacks lasting 4–72 hours with: (1) at least two of the qualifying pain characteristics (unilateral location, pulsating quality, moderate or severe pain intensity, or aggravation by routine physical exertion); and (2) at least one of the associated symptoms (nausea and/or vomiting, photo/phonophobia); and (3) not readily attributed to another central nervous system disorder or head trauma (according to subject self-report). Women who met these criteria are referred to as migraineurs throughout our study. Migraineurs with aura fulfilled all of the aforementioned criteria for definitive migraine in addition to at least two aura attacks consisting of: (1) at least one of the following (fully reversible visual symptoms, fully reversible sensory symptoms, or fully reversible dysphasic speech

disturbance) but no motor weakness; and (2) at least two of the following (homonymous visual symptoms and/or unilateral sensory symptoms, the development of at least one aura symptom that develops gradually over ≥5 minutes, and/or each symptom lasts ≥5 and ≤ 60 minutes). (ICHD, 2004) Using these criteria we categorized migraineurs to either migraineur with aura, or migraineur without aura.

PHQ-9—The PHQ-9 is a self-administered module that ascertains unipolar depression by asking: "Over the last two weeks, how often have you been bothered by any of the following problems". The problems assessed feelings of feigned interest, hopelessness, trouble sleeping, lack of energy, changes in appetite, self-deprecation, trouble concentrating, changes in physical behavior, and thoughts of self-harm. The 9-item instrument asks respondents to rate the relevancy of each statement over the past two weeks on a four-point scale ranging from: (0) not at all, (1) several days, (2) more than half the days, and (3) nearly every day. Scores range from 0 to 27. Validated cutoffs were used to categorize PHQ-9 scores (Kroenke et al., 2001). Briefly, a score of ≥10 on the PHQ-9 is associated with 88% sensitivity and 88% specificity in diagnosing unipolar major depressive disorder (MDD) using the Diagnostic Statistical Manual Fourth Edition criteria (Kroenke et al., 2001). Additionally, we categorized participants as exhibiting minimal (score 0–4), mild (score 5–9), moderate (score 10–14), and severe (score ≥15) depressive symptoms on the PHQ-9 scale.

DASS-21—The DASS-21 is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety, and stress (Depression Anxiety Stress Scales 2013) (Depression Anxiety Stress Scales 2013) (Depression Anxiety Stress Scales 2013). The depression scale assessed dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest or involvement, anhedonia, and inertia; the anxiety scale assessed autonomic arousal, situational anxiety, and subjective experience of anxious affect; and the stress scale assessed difficulty relaxing, nervous arousal, easy agitation, irritability, and impatience (Lovibond, 1998; Lovibond and Lovibond, 1995). The 21-item instrument asks respondents to rate the relevancy of each of the three negative affective states over the past week on a four-point scale ranging from: (0) not at all, (1) some of the time, (2) a good part of the time, and (3) most of the time. Scores range from 0 to 21 in each of the three domains, and are then multiplied by two to produce a possible score of 0 to 42 in each of the three domains. Validated cutoffs were used to categorize DASS scores (Lovibond and Lovibond, 1995). Briefly, we categorized participants as exhibiting minimal (score 0–9), mild (score 10–13), moderate (score 14–20), and severe (score ≥21) depressive symptoms on the DASS Depression subscale. The corresponding cutoffs for the DASS Anxiety subscale were minimal (score 0–7), mild (score 8–9), moderate (score 10–14), and severe (score ≥15). The corresponding cutoffs for the DASS Stress subscale were minimal (score 0–14), mild (score 15–18), moderate (score 19–25), and severe (score ≥26). In addition to the established DASS subscale cutoffs, we further analyzed DASS global quartile scores. Internal consistencies for each scale for the DASS normative sample are: depression 0.91; anxiety 0.84; and stress 0.90 (Lovibond and Lovibond, 1995).

2.3 Other Covariates

Age at last menstrual period was categorized as: <25, 25–34, and ≥35 years. Other variables included: maternal race/ethnicity (non-Hispanic white, African-American, Asian, other), annual household income in U.S. thousands (<50, 50–69, ≥70), single marital status (yes, no), nulliparous (yes, no), unplanned pregnancy (yes, no), cigarette smoker (never, prior, current), family history of headache or migraine (yes, no), and self-reported history of chronic hypertension (yes/no). Pre-pregnancy body mass index (BMI) was calculated from pre-pregnancy height and weight (kg/m^2) and categorized as: <18.5, 18.5–24.9, 25.0–29.9, and ≥30 kg/m^2 based on cutoffs from the WHO Global Database on BMI (WHO, 2006).

2.4 Statistical Analysis

Frequency distributions of maternal sociodemographic, reproductive, medical and behavioral histories were compared by migraine status defined by ICHD-II (no migraine, any migraine), and migraine subtype (no migraine, migraine with aura, migraine without aura). We examined whether mean and inter-quartile scores differed by migraine status and subtype using Student's t-test and the Kruskal-Wallis test respectively. Logistic regression procedures were used to calculate maximum likelihood estimates of odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for potential confounders. Confounding was assessed by entering covariates (Table 1 variables) into the logistic regression model one at a time, and by comparing adjusted ORs (AORs) to unadjusted ORs. Final multivariate logistic regression models included those covariates that altered unadjusted ORs by at least 10%. Covariates in the final model included maternal age, unplanned pregnancy, and maternal pre-pregnancy BMI. In multivariate logistic analysis to test for a linear trend of increasing psychiatric severity we modeled the mood severity variables as continuous. All analyses were performed using Stata 13.1 (Stata College Station, TX) statistical analysis software, and all reported p-values are two-sided and deemed statistically significant at α=0.05.

RESULTS

Based on ICHD-II criteria approximately 28.2% (N=372) of the cohort were classified as having a lifetime history of any migraine. Migraineurs were further categorized as 122 migraineurs with aura and 250 migraineurs without aura. Maternal characteristics according to migraine status are summarized in Table 1. When compared with non-migraineurs, migraineurs were more likely to report a family history of migraine/headache and to have a pre-pregnancy BMI ≥25.0 kg/m^2. Other characteristics including age, race/ethnicity, annual household income, marital status, parity, unplanned pregnancy, smoking status, and history of chronic hypertension were similar for the two study groups.

Table 2 shows mean and median PHQ-9 and DASS-21 summary scores by migraineur status. Compared with non-migraineurs, migraineurs had statistically higher mean PHQ-9 scores (6.2 ± 3.6 vs. 5.3 ± 3.5; p-value <0.001) and mean DASS-21 total scores (19.5 ± 13.9 vs. 15.9 ± 13.1; p-value <0.001). Mean DASS-21 subscale scores were also statistically higher for migraineurs compared to non-migraineurs in all three domains: depression (5.0 ± 5.3 vs. 4.1 ± 4.8; p-value <0.001), anxiety (4.3 ± 4.2 vs. 3.4 ± 4.1; p-value <0.001), and

stress (10.3 ± 6.9 vs. 8.5 ± 6.6; p-value <0.001). The highest mean PHQ-9 and DASS-21 total and sub-scale scores were observed among migraineurs with aura, and were significantly higher to the mean scores of non-migraineurs.

Compared with non-migraineurs, migraineurs were more likely to exhibit mild (AOR= 1.42; 95% CI: 1.09–1.85), moderate (AOR=1.56; 95% CI: 1.06–2.29), and severe depression (AOR=1.95; 95% CI: 0.84–4.57), although the association for severe depression did not reach statistical significance (Table 3). When we combined moderate and severe depression, defined as major depressive disorder (MDD), migraineurs had 1.60-fold higher odds of experiencing depression (AOR=1.60; 95% CI: 1.12–2.31), as measured by a PHQ-9 score ≥10 (Table 3). Migraineurs with aura, as compared with non-migraineurs, were more likely to have moderate depression (AOR=1.76; 95% CI: 0.99–3.11) and severe depression (AOR=3.28; 95% CI: 1.13–9.50). The corresponding AORs for migraineurs without aura were lower and statistically nonsignificant (Table 3).

Migraineurs, as compared with non-migraineurs had higher odds of depressive, anxiety and stress symptoms as measured using the DASS-21 questionnaire (Table 4). The adjusted odds and 95% CI for successive quartiles of the global DASS-21 score associated with history of migraine were: Q2: 1.32 (0.89–1.95), Q3: 1.82 (1.25–2.64), and Q4: 2.30 (1.60–3.30) with the lowest quartile as the referent group (p-value for trend < 0.001). Associations were notably stronger for migraineurs with aura as compared with non-migraineurs. Similar patterns of associations were observed when we repeated analyses for each of the DASS-21 subscales for anxiety and stress symptoms.

DISCUSSION

Overall we found that compared with non-migraineurs, migraineurs were more likely to have unipolar depression, anxiety, and stress as measured by the PHQ-9 and DASS-21. The odds of MDD, severe anxiety, and severe stress symptoms were particularly elevated among migraineurs with aura. Our results are in accordance with previous reports indicating an increased prevalence of affective disorders among individuals with headache or migraine, albeit generally in non-pregnant adult populations and adolescents (Breslau et al., 1994; Breslau et al., 2003; Fuller-Thomson et al., 2013; Gelaye et al., 2013; Jette et al., 2008; Kalaydjian and Merikangas, 2008; McWilliams et al., 2004; Merikangas et al., 1990; Patel et al., 2004; Saunders et al., 2014; Swartz et al., 2000; Zwart et al., 2003). Furthermore, our results are also in accordance with the two other studies that have reported on observations of such associations in pregnant women (Cripe et al., 2010; Williams et al., 2010), and thus extends this literature.

Our observation of nearly two-fold increased odds of unipolar depression (PHQ-9 ≥10) (AOR=1.60; 95% CI: 1.12–2.31) and severe stress (AOR=2.01; 95% CI: 0.98–4.12) among migraineurs compared to non-migraineurs are consistent with the limited number of studies that have reported on the association between migraine and depression, and migraine and perceived stress in pregnant populations (Cripe et al., 2010; Williams et al., 2010). In a study of 2,293 pregnant women in Peru, the odds of moderate to severe depressive symptoms (PHQ-9 score 10–27) among women with strict migraine was 2.06 times that of

women without a history of migraine (AOR=2.06; 95% CI: 1.54–2.76) adjusted for maternal age and race (Cripe et al., 2010). The odds of moderate (PHQ-9 score 10–14), moderately severe (PHQ-9 score 15–19), and severe depression (PHQ-9 score 20–27) during pregnancy were also significantly higher and nearly twofold among women with strict migraine when compared to women without a history of migraine; AOR=2.12; 95% CI: 1.54–2.93, AOR=1.85; 95% CI: 1.16–2.96, and AOR=2.23; 95% CI: 1.08–4.62, respectively. In another study of women delivering in Seattle, Washington, we (2010) noted that migraine (based on self-reports of a clinical diagnosis) was associated with 1.57-increased odds of perceived stress in the past 3-months (based on a Perceived Stress Scale score ≥7) compared to non-migraineurs, (AOR=1.57; 95% CI 1.06–2.31), adjusted for parity, history of pre-gestational hypertension and pre-pregnancy body mass index (Williams et al., 2010). Taken together, these increased odds provide evidence of a mood-migraine association among pregnant women.

Our prevalence estimates of lifetime history of migraine (28.2%) are somewhat higher than previous estimates from other pregnancy cohorts (9–20%), (Adeney et al., 2006; Frederick et al., 2014) yet comparable to the 2011 National Health Interview Survey's three-month prevalence of migraine or other severe headache among women of reproductive age (26.1%) (Smitherman et al., 2013). Although slightly attenuated, our observations are also concordant with other cross-sectional population-level studies across North America reporting on associations between migraine and mood disorders in non-pregnant populations. In a recent Canadian study, women migraineurs (based on self-report of a clinical diagnosis) had 1.89-increased odds of depression over a period of at least two-weeks in the previous year (based on the Composite International Diagnostic Interview-Short Form, CIDI-SF) compared to women without migraine, adjusting for sociodemographic and disability covariates (OR=1.89; 95% CI: 1.71–2.10) (Fuller-Thomson et al., 2013). In a nationally representative sample of the U.S. from 1999–2004 adults who self-reported severe headache or migraine had nearly three-fold increased odds of depression and generalized anxiety disorder (GAD) (as measured by the WHO CIDI) compared to individuals who did not self-report severe headache or migraine, (depression AOR=2.84; 95% CI: 1.71–4.73 and GAD AOR=3.03; 95% CI: 1.43–6.38) adjusting for age, race, sex, and education status (Kalaydjian and Merikangas, 2008). In another U.S. study in Baltimore, Swartz et.al (2000) reported that the odds of lifetime history of major depression (as measured by the National Institute of Mental Health Diagnostic Interview Schedule) was 2.25 times higher among migraineurs (as measured using an interviewer-administered survey based on ICHD-II criteria) compared to self-reported non-migraineurs (95% CI: 1.43–3.54), adjusting for age and sex (Swartz et al., 2000). Although our current study inquired about unipolar depression, bipolar depression is a well-recognized co-morbid condition with migraine in studies mostly conducted among men and non-pregnant women (Dilsaver et al., 2009a; Dilsaver et al., 2009b, c; Peterlin and Ward, 2005). For instance Dilsaver et al in their study among Latino adolescents of Mexican American origin found that those with bipolar depression were 6.15-times as likely (OR=6.15, 95% CI = 1.25–30.4) to have migraine headache than those in the control group (Dilsaver et al., 2009c). Future research evaluating the neurobiology of bipolar depression in pregnancy is warranted.

The pathogenesis for comorbid migraine-mood disorders remains unclear. Common neuropathology of the serotoninergic and dopaminergic systems has been proposed, (D'Andrea et al., 1989; Frediani and Villani, 2007) as well as dysregulation of the hypothalamic-pituitary adrenalin (HPA) axis (McWilliams et al., 2004; Overeem et al., 2002). Increased secretion of corticotrophin-releasing factor and changes in cortisol secretion may additionally play a role in the pathophysiology of migraine and mood disorders (Overeem et al., 2002). It has also been proposed that stress and depression affect inflammatory immune parameters and endothelial functioning during pregnancy, (Christian, 2014; Christian et al., 2009) and that neurogenic inflammation plays a role in migraine pathogenesis (Brietzke et al., 2012; Geppetti et al., 2005). Other plausible mechanisms include shared genetics and environmental trigger factors, or that a causal relationship between migraine and mood disorders exists (Ligthart et al., 2014; Martin et al., 2005). However the directionality of a causal relationship also remains unclear. Studies that favor the shared pathophysiological mechanism explanation suggest that each disorder increases the risk for the first onset of the other (Breslau et al., 1994). Until a general consensus is reached regarding the biological mechanisms of migraine-mood disorders their comorbidity continues to affect the quality of life, total disability, and therapeutic drug strategies for such patients (Finocchi et al., 2010). Additionally, this comorbidity may adversely affect birthing outcomes and childrearing if left untreated among pregnant women.

Several important limitations should be considered when interpreting our results. First, our cross-sectional study design prohibits clarification of temporality of the association between migraine and symptoms of mood disorders, as well as our ability to make statements regarding the role of pregnancy. Longitudinal studies with prospective clinical assessments of mood-migraine symptoms during the pre-conception, antepartum and early postpartum periods are needed to understand the underlying mechanisms of this association and to pinpoint optimal screening windows. Second, despite our use of validated instruments and trained interviewers, participants did not receive formal clinical evaluation and diagnoses for migraine and mood disorders, thus we cannot rule out some misclassification errors. However, such errors are likely to have resulted in an attenuation of estimated associations. Third, our sample was comprised of few women who endorsed severe psychiatric symptomology, likely resulting in a reduction of the precision of our estimates, as reflected by the 95% confidence intervals reported in some instances. Lastly, in our study we adjusted for putative confounders. However, as with all observational studies, we cannot rule out the possibility of residual confounding by unmeasured covariates such as maternal medication use.

In summary, we found increased odds of unipolar mood disorders among pregnant migraineurs compared with pregnant non-migraineurs. The odds of mood disorders were particularly elevated among migraineurs with aura. Our findings supports the need for prospective studies designed to (1) enhance the understanding of the biological mechanisms underlying these observed associations; and (2) develop and evaluate the clinical effectiveness of integrated somatic and mental antepartum screening and treatment strategies that mitigate the burden of these highly comorbid conditions in pregnant women.

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References

Adeney KL, Flores JL, Perez JC, Sanchez SE, Williams MA. Prevalence and correlates of migraine among women attending a prenatal care clinic in Lima, Peru. Cephalalgia. 2006; 26:1089–1096. [PubMed: 16919059]

Adeney KL, Williams MA. Migraine headaches and preeclampsia: an epidemiologic review. Headache. 2006; 46:794–803. [PubMed: 16643583]

Breslau N, Davis GC, Schultz LR, Peterson EL. Joint 1994 Wolff Award Presentation. Migraine and major depression: a longitudinal study. Headache. 1994; 34:387–393. [PubMed: 7928322]

Breslau N, Lipton RB, Stewart WF, Schultz LR, Welch KM. Comorbidity of migraine and depression: investigating potential etiology and prognosis. Neurology. 2003; 60:1308–1312. [PubMed: 12707434]

Brietzke E, Mansur RB, Grassi-Oliveira R, Soczynska JK, McIntyre RS. Inflammatory cytokines as an underlying mechanism of the comorbidity between bipolar disorder and migraine. Medical Hypotheses. 2012; 78:601–605. [PubMed: 22365650]

Buse DC, Loder EW, Gorman JA, Stewart WF, Reed ML, Fanning KM, Serrano D, Lipton RB. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) Study. Headache. 2013; 53:1278–1299. [PubMed: 23808666]

Chen HM, Chen SF, Chen YH, Lin HC. Increased risk of adverse pregnancy outcomes for women with migraines: a nationwide population-based study. Cephalalgia. 2010; 30:433–438. [PubMed: 19614685]

Christian LM. Effects of stress and depression on inflammatory immune parameters in pregnancy. American Journal of Obstetrics and Gynecology. 2014

Christian LM, Franco A, Glaser R, Iams JD. Depressive symptoms are associated with elevated serum proinflammatory cytokines among pregnant women. Brain, Behavior, and Immunity. 2009; 23:750–754.

Cripe SM, Frederick IO, Qiu C, Williams MA. Risk of preterm delivery and hypertensive disorders of pregnancy in relation to maternal co-morbid mood and migraine disorders during pregnancy. Paediatric and Perinatal Epidemiology. 2011; 25:116–123. [PubMed: 21281324]

Cripe SM, Sanchez S, Lam N, Sanchez E, Ojeda N, Tacuri S, Segura C, Williams MA. Depressive symptoms and migraine comorbidity among pregnant Peruvian women. Journal of Affective Disorders. 2010; 122:149–153. [PubMed: 19695709]

D'Andrea G, Welch KM, Riddle JM, Grunfeld S, Joseph R. Platelet serotonin metabolism and ultrastructure in migraine. Archives of neurology. 1989; 46:1187–1189. [PubMed: 2479367]

de Paz NC, Sanchez SE, Huaman LE, Chang GD, Pacora PN, Garcia PJ, Ananth CV, Qiu C, Williams MA. Risk of placental abruption in relation to maternal depressive, anxiety and stress symptoms. Journal of Affective Disorders. 2011; 130:280–284. [PubMed: 20692040]

Depression Anxiety Stress Scales, D. Psychology Foundation of Australia. 2013

Dilsaver SC, Benazzi F, Oedegaard KJ, Fasmer OB, Akiskal HS. Is a family history of bipolar disorder a risk factor for migraine among affectively ill patients? Psychopathology. 2009a; 42:119–123. [PubMed: 19246955]

Dilsaver SC, Benazzi F, Oedegaard KJ, Fasmer OB, Akiskal KK, Akiskal HS. Migraine headache in affectively ill latino adults of mexican american origin is associated with bipolarity. Primary Care cCmpanion to the Journal of Clinical Psychiatry. 2009b; 11:302–306.

Dilsaver SC, Benazzi F, Oedegaard KJ, Fasmer OB, Akiskal KK, Akiskal HS. Migraine in affectively ill Mexican adolescents. World Psychiatry. 2009c; 8:37–39. [PubMed: 20157635]

Farias DR, Pinto Tde J, Teofilo MM, Vilela AA, Vaz Jdos S, Nardi AE, Kac G. Prevalence of psychiatric disorders in the first trimester of pregnancy and factors associated with current suicide risk. Psychiatry Research. 2013; 210:962–968. [PubMed: 24090486]

Finocchi C, Villani V, Casucci G. Therapeutic strategies in migraine patients with mood and anxiety disorders: clinical evidence. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2010; 31(Suppl 1):S95–S98.

Frederick IO, Qiu C, Enquobahrie DA, Aurora SK, Peterlin BL, Gelaye B, Williams MA. Lifetime prevalence and correlates of migraine among women in a pacific northwest pregnancy cohort study. Headache. 2014; 54:675–685. [PubMed: 23992560]

Frediani F, Villani V. Migraine and depression. Neurological Sciences. 2007; 28(Suppl 2):S161–S165. [PubMed: 17508165]

Fuller-Thomson E, Schrumm M, Brennenstuhl S. Migraine and Despair: Factors Associated with Depression and Suicidal Ideation among Canadian Migraineurs in a Population-Based Study. Depression Research and Treatment. 2013; 2013:401487. [PubMed: 24224086]

Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstetrics and Gynecology. 2005; 106:1071–1083. [PubMed: 16260528]

Gelaye B, Peterlin BL, Lemma S, Tesfaye M, Berhane Y, Williams MA. Migraine and psychiatric comorbidities among sub-saharan african adults. Headache. 2013; 53:310–321. [PubMed: 23095087]

Geppetti P, Capone JG, Trevisani M, Nicoletti P, Zagli G, Tola MR. CGRP and migraine: neurogenic inflammation revisited. Journal of Headache and Pain. 2005; 6:61–70. [PubMed: 16362644]

Graignic-Philippe R, Dayan J, Chokron S, Jacquet AY, Tordjman S. Effects of prenatal stress on fetal and child development: A critical literature review. Neuroscience and Biobehavioral Reviews. 2014; 43C:137–162. [PubMed: 24747487]

ICHD. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004; 24(Suppl 1):9–160. [PubMed: 14979299]

Jette N, Patten S, Williams J, Becker W, Wiebe S. Comorbidity of migraine and psychiatric disorders--a national population-based study. Headache. 2008; 48:501–516. [PubMed: 18070059]

Kalaydjian A, Merikangas K. Physical and mental comorbidity of headache in a nationally representative sample of US adults. Psychosomatic Medicine. 2008; 70:773–780. [PubMed: 18725426]

Kirchmann M, Seven E, Bjornsson A, Bjornssdottir G, Gulcher JR, Stefansson K, Olesen J. Validation of the deCODE Migraine Questionnaire (DMQ3) for use in genetic studies. European journal of Neurology. 2006; 13:1239–1244. [PubMed: 17038039]

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of General Internal Medicine. 2001; 16:606–613. [PubMed: 11556941]

Lee AM, Lam SK, Sze Mun Lau SM, Chong CS, Chui HW, Fong DY. Prevalence, course, and risk factors for antenatal anxiety and depression. Obstetrics and Gynecology. 2007; 110:1102–1112. [PubMed: 17978126]

Ligthart L, Hottenga JJ, Lewis CM, Farmer AE, Craig IW, Breen G, Willemsen G, Vink JM, Middeldorp CM, Byrne EM, Heath AC, Madden PA, Pergadia ML, Montgomery GW, Martin NG, Penninx BW, McGuffin P, Boomsma DI, Nyholt DR. Genetic risk score analysis indicates migraine with and without comorbid depression are genetically different disorders. Human Genetics. 2014; 133:173–186. [PubMed: 24081561]

Lovibond PF. Long-term stability of depression, anxiety, and stress syndromes. Journal of Abnormal Psychology. 1998; 107:520–526. [PubMed: 9715586]

Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behaviour Research and Therapy. 1995; 33:335–343. [PubMed: 7726811]

Marozio L, Facchinetti F, Allais G, Nappi RE, Enrietti M, Neri I, Picardo E, Benedetto C. Headache and adverse pregnancy outcomes: a prospective study. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2012; 161:140–143.

Martin PR, Todd J, Reece J. Effects of noise and a stressor on head pain. Headache. 2005; 45:1353–1364. [PubMed: 16324168]

McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: results from a nationally representative sample. Pain. 2004; 111:77–83. [PubMed: 15327811]

Meades R, Ayers S. Anxiety measures validated in perinatal populations: a systematic review. Journal of Affective Disorders. 2011; 133:1–15. [PubMed: 21078523]

Merikangas KR, Angst J, Isler H. Migraine and psychopathology. Results of the Zurich cohort study of young adults. Archives of General Psychiatry. 1990; 47:849–853. [PubMed: 2393343]

Nguyen TV, Low NC. Comorbidity of migraine and mood episodes in a nationally representative population-based sample. Headache. 2013; 53:498–506. [PubMed: 23095134]

O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. Best practice & research. Clinical obstetrics & gynaecology. 2014; 28:3–12. [PubMed: 24140480]

Overeem S, van Vliet JA, Lammers GJ, Zitman FG, Swaab DF, Ferrari MD. The hypothalamus in episodic brain disorders. The Lancet. Neurology. 2002; 1:437–444. [PubMed: 12849366]

Patel NV, Bigal ME, Kolodner KB, Leotta C, Lafata JE, Lipton RB. Prevalence and impact of migraine and probable migraine in a health plan. Neurology. 2004; 63:1432–1438. [PubMed: 15505161]

Peterlin BL, Ward TN. Neuropsychiatric aspects of migraine. Current Psychiatry Reports. 2005; 7:371–375. [PubMed: 16216157]

Rubertsson C, Hellstrom J, Cross M, Sydsjo G. Anxiety in early pregnancy: prevalence and contributing factors. Archives of women's mental health. 2014; 17:221–228.

Sanchez SE, Puente GC, Atencio G, Qiu C, Yanez D, Gelaye B, Williams MA. Risk of spontaneous preterm birth in relation to maternal depressive, anxiety, and stress symptoms. The Journal of reproductive medicine. 2013; 58:25–33. [PubMed: 23447915]

Sanchez SE, Williams MA, Pacora PN, Ananth CV, Qiu C, Aurora SK, Sorensen TK. Risk of placental abruption in relation to migraines and headaches. BMC women's health. 2010; 10:30. [PubMed: 20977769]

Satyanarayana VA, Lukose A, Srinivasan K. Maternal mental health in pregnancy and child behavior. Indian journal of psychiatry. 2011; 53:351–361. [PubMed: 22303046]

Saunders EF, Nazir R, Kamali M, Ryan KA, Evans S, Langenecker S, Gelenberg AJ, McInnis MG. Gender differences, clinical correlates, and longitudinal outcome of bipolar disorder with comorbid migraine. Journal of Clinical Psychiatry. 2014

Smitherman TA, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache. 2013; 53:427–436. [PubMed: 23470015]

Spitzer RL, Williams JB, Kroenke K, Hornyak R, McMurray J. Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. American Journal of Obstetrics and Gynecology. 2000; 183:759–769. [PubMed: 10992206]

Swartz KL, Pratt LA, Armenian HK, Lee LC, Eaton WW. Mental disorders and the incidence of migraine headaches in a community sample: results from the Baltimore Epidemiologic Catchment area follow-up study. Archives of General Psychiatry. 2000; 57:945–950. [PubMed: 11015812]

Szegda K, Markenson G, Bertone-Johnson ER, Chasan-Taber L. Depression during pregnancy: a risk factor for adverse neonatal outcomes? A critical review of the literature. Journal of Maternal-fetal & Neonatal Medicine. 2014; 27:960–967. [PubMed: 24044422]

WHO. [Accessed on 10/06/2014] World Health Organization. Global Database on Body Mass Index. 2006. Available at: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html

WHO. [Accessed on 10/06/2014] World Health Organization. Atlas of Headache Disorders and Resourcces in the World. 2011. Available at: http://www.who.int/mental_health/management/atlas_headache_disorders/en/

WHO. [Accessed on 10/06/2014] World Health Organization. Headache Disorders. 2012. Available at: http://www.who.int/mediacentre/factsheets/fs277/en/

Williams MA, Aurora SK, Frederick IO, Qiu C, Gelaye B, Cripe SM. Sleep duration, vital exhaustion and perceived stress among pregnant migraineurs and non-migraineurs. BMC Pregnancy and Childbirth. 2010; 10:72. [PubMed: 21047418]

Williams MA, Peterlin BL, Gelaye B, Enquobahrie DA, Miller RS, Aurora SK. Trimester-specific blood pressure levels and hypertensive disorders among pregnant migraineurs. Headache. 2011; 51:1468–1482. [PubMed: 21797858]

Wisner KL, Sit DK, McShea MC, Rizzo DM, Zoretich RA, Hughes CL, Eng HF, Luther JF, Wisniewski SR, Costantino ML, Confer AL, Moses-Kolko EL, Famy CS, Hanusa BH. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. JAMA Psychiatry. 2013; 70:490–498. [PubMed: 23487258]

Woods SM, Melville JL, Guo Y, Fan MY, Gavin A. Psychosocial stress during pregnancy. American Journal of Obstetrics and Gynecology. 2010; 202:61. e61–67. [PubMed: 19766975]

Zhong Q, Gelaye B, Rondon M, S ES, P JG, Sanchez E, Y VB, G ES, D CH, May Cripe S, M AW. Comparative performance of Patient Health Questionnaire-9 and Edinburgh Postnatal Depression Scale for screening antepartum depression. Journal of Affective Disorders. 2014; 162:1–7. [PubMed: 24766996]

Zwart JA, Dyb G, Hagen K, Odegard KJ, Dahl AA, Bovim G, Stovner LJ. Depression and anxiety disorders associated with headache frequency. The Nord-Trondelag Health Study. European Journal of Neurology. 2003; 10:147–152. [PubMed: 12603289]

Table 1

Characteristics of the Study Population According to Migraine Status

Characteristics	No Migraine (N=949)	Any Migraine (N=372)	*Migraine with Aura (N=122)*	*Migraine without Aura (N=250)*
Maternal Age (years)	33.4 ± 4.1	33.1 ± 4.3	*33.0 ± 4.8*	*33.2 ± 4.0*
<25	5 (0.5)	7 (1.9)	*5 (4.1)*	*2 (0.8)*
25 – 34	595 (62.7)	235 (63.2)	*73 (59.8)*	*162 (64.8)*
≥ 35	349 (36.8)	130 (34.9)	*44 (36.1)*	*86 (34.4)*
Maternal Race/Ethnicity				
Non-Hispanic White	770 (81.1)	310 (83.3)	*104 (85.3)*	*206 (82.4)*
African American	14 (1.5)	6 (1.6)	*3 (2.5)*	*3 (1.2)*
Asian	110 (11.6)	33 (8.9)	*8 (6.6)*	*25 (10.0)*
Other	55 (5.8)	23 (6.2)	*7 (5.7)*	*16 (6.4)*
Annual Household Income ($)				
<50,000	24 (2.5)	12 (3.2)	*8 (6.6)*	*4 (1.6)*
50,000–69,000	48(5.1)	22 (5.9)	*6 (4.9)*	*16 (6.4)*
≥ 70,000	845 (89.0)	329 (88.4)	*105 (86.1)*	*224 (89.6)*
Not Reported	32 (3.4)	9 (2.4)	*3 (2.5)*	*6 (2.4)*
Single Marital Status	75 (7.9)	29 (7.8)	*11 (9.0)*	*18 (7.2)*
Nulliparous	507 (53.4)	190(51.1)	*59 (48.4)*	*131 (52.4)*
Unplanned Pregnancy	114 (12.0)	50 (13.4)	*24 (19.7)*	*26 (10.4)*
Cigarette Smoker				
Never	711 (74.9)	274 (73.7)	*92 (75.4)*	*182 (72.8)*
Prior	201 (21.2)	83 (22.3)	*24 (19.7)*	*59 (23.6)*
Current	37 (3.9)	15 (4.0)	*6 (4.9)*	*9 (3.6)*
Family History of Headache/Migraine*	311 (32.8)	232 (62.4)	*82 (67.2)*	*150 (60.0)*
History of Chronic Hypertension	14 (1.5)	11 (3.0)	*3 (2.5)*	*8 (3.2)*
Pre-Pregnancy Body Mass Index (kg/m^2)*	23.3 ± 4.0	24.0 ± 4.9	*24.0 ± 4.8*	*23.3 ± 4.0*
<18.5	29 (3.1)	12 (3.2)	*2 (1.6)*	*10 (4.0)*
18.5–24.9	694 (73.1)	245 (65.9)	*83 (68.0)*	*162 (64.8)*
25.0–29.9	170 (17.9)	79 (21.2)	*26 (21.3)*	*53 (21.2)*
≥ 30.0	56 (5.9)	36 (9.7)	*11 (9.0)*	*25 (10.0)*

Data in mean ± SD or number (%)

* P-value from ANOVA <0.05 for no migraine vs. migraine with aura, migraine without aura

Table 2

Summary of Patient Health Questionnaire-9 (PHQ-9) Score and Depression Anxiety Stress Scale (DASS) Scores According to Migraine Status

Index	No Migraine (N=949)	Any Migraine (N=372)	*Migraine with Aura (N=122)*	*Migraine without Aura (N=250)*	*P-value***
Depression PHQ-9 Total Score					
Mean ± SD	5.3 ± 3.5	6.2 ± 3.6*	*6.6 ± 3.8*	*6.0 ± 3.5*	*<0.001*
Median (IQR)	5 (3–7)	6 (3–9)*	*6 (3–9)*	*5 (3–8)*	*<0.001*
DASS Total Score					
Mean ± SD	15.9 ± 13.1	19.5 ± 13.9*	*22.7 ± 16.3*	*18.0 ± 12.4*	*<0.001*
Median (IQR)	14 (8–22)	16 (10–26)*	*20 (12–30)*	*16 (10–24)*	*<0.001*
DASS Depression Sub-scale Score					
Mean ± SD	4.1 ± 4.8	5.0 ± 5.3*	*6.0 ± 5.9*	*4.5 ± 4.9*	*<0.001*
Median (IQR)	2 (0–6)	4 (2–8)*	*4 (2–8)*	*4 (2–6)*	*<0.001*
DASS Anxiety Sub-scale Score					
Mean ± SD	3.4 ± 4.1	4.3 ± 4.2*	*5.2 ± 5.2*	*3.8 ± 3.6*	*<0.001*
Median (IQR)	2 (0–4)	4 (2–6)*	*4 (2–8)*	*4 (0–6)*	*<0.001*
DASS Stress Sub-scale Score					
Mean ± SD	8.5 ± 6.6	10.3 ± 6.9*	*11.5 ± 7.9*	*9.7 ± 6.4*	*<0.001*
Median (IQR)	8 (4–12)	10 (6–14)*	*10 (6–16)*	*10 (4–14)*	*<0.001*

* P-value <0.05 in 2-sample student t test comparing any migraine versus no migraine

** P-value from ANOVA or Kruskal-Wallis non-parametric ANOVA

Table 3

Adjusted Odds Ratio (AOR) and 95% Confidence Interval (CI) for Depression Symptom Severity According to Migraine Status

	No Migraine (N=949)	Any Migraine (N=372)		*Migraine with Aura (N=122)*		*Migraine without Aura (N=250)*	
Depressive Symptoms	**n (%)**	**n (%)**	**AOR (95% CI)**	***n (%)***	***AOR (95% CI)***	***n (%)***	***AOR (95% CI)***
PHQ-9 Total Score							
Minimal (0–4)	454 (47.8)	141 (37.9)	1.00 (referent)	*46 (37.7)*	*1.00 (referent)*	*95 (38.0)*	*1.00 (referent)*
Mild (5–9)	375 (39.5)	170 (45.7)	1.42 (1.09–1.85)	*51 (41.8)*	*1.32 (0.86–2.02)*	*119 (47.6)*	*1.47 (1.09–2.00)*
Moderate (10–14)	105 (11.1)	52 (14.0)	1.56 (1.06–2.29)	*20 (16.4)*	*1.76 (0.99–3.11)*	*32 (12.8)*	*1.45 (0.92–2.29)*
Severe (≥15)	15 (1.6)	9 (2.4)	1.95 (0.84–4.57)	*5 (4.1)*	*3.28 (1.13–9.50)*	*4 (1.6)*	*1.30 (0.42–4.01)*
p-value for trend			*0.002*		*0.008*		*0.032*
PHQ-9 Total Score							
Minimal (0–4)	454 (47.8)	141 (37.9)	1.00 (referent)	*46 (37.7)*	*1.00 (referent)*	*95 (38.0)*	*1.00 (referent)*
Mild (5–9)	375 (39.5)	170 (45.7)	1.42 (1.09–1.85)	*51 (41.8)*	*1.32 (0.86–2.02)*	*119 (47.6)*	*1.47 (1.09–2.00)*
MDD (≥10)	120 (12.7)	61 (16.4)	1.60 (1.12–2.31)	*25 (20.5)*	*1.94 (1.14–3.30)*	*36 (14.4)*	*1.43 (0.93–2.21)*
p-value for trend			*0.003*		*0.014*		*0.024*

Adjusted for maternal age, unplanned pregnancy and maternal pre-pregnancy body mass index (BMI)

Table 4

Adjusted Odds Ratios (AOR) and 95% Confidence Intervals (CM for Psvchiatric Characteristics According to Migraine Status

DASS Items	No migraine (N=949)	Any Migraine (N=372)		Migraine with Aura (N=122)		Migraine without Aura (N=250)	
	n (%)	n (%)	AOR (95% CI)	*n (%)*	*AOR (95% CI)*	*n (%)*	*AOR (95% CI)*
DASS Global Quartile							
Q1 (<8)	234 (24.6)	56 (15.1)	1.00 (referent)	*15 (12.3)*	*1.00 (referent)*	*41 (16.4)*	*1.00 (referent)*
Q2 (8–12)	235 (24.8)	75 (20.2)	1.32 (0.89–1.95)	*20 (16.4)*	*1.33 (0.66–2.66)*	*55 (22.0)*	*1.31 (0.84–2.04)*
Q3 (13–20)	237 (25.0)	103 (27.7)	1.82 (1.25–2.64)	*31 (25.4)*	*2.04 (1.07–3.88)*	*72 (28.8)*	*1.74 (1.14–2.66)*
Q4 (≥21)	243 (25.6)	138 (37.1)	2.30 (1.60–3.30)	*56 (45.9)*	*3.38 (1.85–6.16)*	*82 (32.8)*	*1.90 (1.25–2.89)*
p-value for trend			*<0.001*		*<0.001*		*0.001*
DASS Depression Sub-Scale							
Minimal (0–9)	825 (86.9)	309 (83.1)	1.00 (referent)	*96 (78.7)*	*1.00 (referent)*	*213 (85.2)*	*1.00 (referent)*
Mild (10–13)	72 (7.6)	37 (9.9)	1.33 (0.88–2.03)	*11 (9.0)*	*1.25 (0.64–2.44)*	*26 (10.4)*	*1.37 (0.85–2.21)*
Moderate (14–20)	43 (4.5)	18 (4.8)	1.14 (0.65–2.02)	*13 (10.7)*	*2.57 (1.33–4.99)*	*5 (2.0)*	*0.47 (0.18–1.20)*
Severe (≥21)	9 (1.0)	8 (2.2)	2.18 (0.83–5.73)	*2 (1.6)*	*1.69 (0.36–7.99)*	*6 (2.4)*	*2.43 (0.85–6.92)*
p-value for trend			*0.082*		*0.011*		*0.601*
DASS Anxiety Sub-Scale							
Minimal (0–7)	816 (86.0)	291 (78.2)	1.00 (referent)	*88 (72.1)*	*1.00 (referent)*	*203 (81.2)*	*1.00 (referent)*
Mild (8–9)	52 (5.5)	39 (10.5)	2.05 (1.32–3.17)	*12 (9.8)*	*2.06 (1.05–4.01)*	*27 (10.8)*	*2.05 (1.25–3.34)*
Moderate (10–14)	59 (6.2)	31 (8.3)	1.42 (0.90–2.25)	*13 (10.7)*	*1.95 (1.02–3.74)*	*18 (7.2)*	*1.19 (0.69–2.07)*
Severe (≥15)	22 (2.3)	11 (3.0)	1.38 (0.66–2.90)	*9 (7.4)*	*3.47 (1.53–7.88)*	*2 (0.8)*	*0.38 (0.09–1.62)*
p-value for trend			*0.015*		*<0.001*		*0.599*
DASS Stress Sub-Scale							
Minimal (0–14)	803 (84.6)	292 (78.5)	1.00 (referent)	*87 (71.3)*	*1.00 (referent)*	*205 (82.0)*	*1.00 (referent)*
Mild (15–18)	85 (9.0)	040 (10.7)	1.25 (0.84–1.87)	*15 (12.3)*	*1.51 (0.83–2.75)*	*25 (10.0)*	*1.14 (0.71–1.83)*
Moderate (19–25)	43 (4.5)	26 (7.0)	1.61 (0.97–2.68)	*11 (9.0)*	*2.22 (1.10–4.48)*	*15 (6.0)*	*1.35 (0.73–2.48)*
Severe (≥26)	18 (1.9)	14 (3.8)	2.01 (0.98–4.12)	*9 (7.4)*	*4.19 (1.81–9.71)*	*5 (2.0)*	*1.05 (0.38–2.86)*
p-value for trend			*0.007*		*<0.001*		*0.396*

Adjusted for maternal age, unplanned pregnancy and maternal pre-pregnancy body mass index (BMI)