Association of migraine headaches with suicidal ideation among pregnant women in Lima, Peru

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Abstract

Background—Suicide is a leading cause of maternal death globally, and suicide prevalence rates have been shown to be increased in those with migraine. No previous study has examined the association between migraine and suicidal ideation during pregnancy.

Objective—To examine the association between migraine and suicidal ideation among a cohort of pregnant women.

Methods—A cross-sectional study was conducted among 3,372 pregnant women attending prenatal care clinics in Lima, Peru. Suicidal ideation and depression were assessed using the Patient Health Questionnaire-9 (PHQ-9) scale during early pregnancy. Migraine classification (including migraine and probable migraine) was based on International Classification of Headache Disorders (ICHD)-III beta criteria. Multivariable logistic regression analyses were performed to estimate odd ratios (OR) and 95% confidence intervals (95%CI).

Results—Suicidal ideation was more common among those with migraine (25.6%) as compared to those with probable migraine (22.1%, p<0.001) or non-migraineurs (12.3%, p<0.001). After adjusting for confounders, including depression, those with migraine or probable migraine had a 78% increased odds of suicidal ideation (OR=1.78; 95%CI: 1.46–2.17), as compared with non-migraineurs. Women with both migraine and depression had a 4.14-fold increased odds of suicidal ideation (OR=4.14; 95%CI: 3.17–5.42) compared to those with neither condition.

Conclusion—Migraine is associated with increased odds of suicidal ideation in pregnant women even when controlling for depression. These findings support the consideration of screening women with comorbid migraine and depression for suicidal behavior during pregnancy.

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Keywords

Migraine; Depression; Suicidal Ideation; Pregnancy

Introduction

Migraine headaches are an often debilitating neurologic disorder with an estimated worldwide prevalence of 10–15% [1, 2]. Migraine is most common among adults 18 to 49 years old [3, 4] as compared to those at either ends of the age distribution, and among women as compared to men [5, 6]. Additionally migraine has been shown to be comorbid with several psychiatric disorders including depression and suicide [7–9]. Suicide is currently a leading cause of maternal death in developed countries [10, 11] and in low and middle income countries [12, 13]. Estimated rates of suicide vary widely between countries [14]. Suicidal behaviors, including suicidal ideation, having a suicide plan, and unsuccessful suicide attempts, are the strongest predictors of suicide. While suicidal ideation is often a defining symptom of depressive disorders, suicidal ideation may occur *without* accompanying depression [15, 16]. Notably, recent studies have demonstrated that a substantial proportion of pregnant women with suicidal ideation do not meet clinical thresholds for depressive disorders [17, 18].

There is limited evidence concerning the association of migraine with suicidal ideation in pregnancy [19]. Therefore, we sought to examine the extent to which migraine is associated with suicidal ideation among a cohort of pregnant women in Peru. Furthermore, we sought to explore the independent and joint effects of migraine and depression on the odds of suicidal ideation.

Methods

Study Population

The study population was a cohort of 3,372 participants from a larger ongoing cohort of the Pregnancy Outcomes, Maternal and Infant Study (PrOMIS). The PrOMIS cohort was designed to examine maternal social and behavioral risk factors of preterm birth and adverse pregnancy outcomes among Peruvian women [20–23]. The study population includes women attending prenatal care clinics enrolled in the Instituto Nacional Materno Perinatal (INMP) in Lima, Peru. The INMP is the primary reference establishment for both maternal and perinatal care operated by the Ministry of Health of the Peruvian government. Recruitment began in February 2012. Pregnant women were eligible for inclusion if they were between the ages of 18 and 49 years, with a gestational age 16 weeks, and who spoke and understood Spanish. All participants provided written informed consent, and all study procedures were approved by Institutional Review Boards from the INMP, Lima, Peru and the Human Research Administration Office at the Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA.

Analytical Population

The study population for this report is derived from information collected from participants who enrolled in the PrOMIS Study between February 2012 and March 2014. During this period 3,775 eligible women were approached, and 3,372 (89.3%) agreed to participate. Forty three (1.2%) women were excluded for missing information on the suicide ideation question on the PHQ-9 questionnaire (thoughts that you would be better off dead or of hurting yourself in some way). Of the 43 participants with missing information on the suicidal ideation question, 35 participants had missing information on other items of the PHQ-9. Twenty-two women were excluded for missing information on their migraine history. A total of 3,323 pregnant women remained for analysis. The excluded participants did not differ from the rest of the cohort in regards to sociodemographic or lifestyle characteristics.

Migraine Assessment

Migraine was classified by trained interviewers using a Spanish-language questionnaire, administered during early pregnancy, and based on the International Classification of Headache Disorders (ICHD)-III beta criteria [24]. Probable migraine was classified as those fulfilling all but one of the migraine diagnostic criteria.

Suicidal Ideation and Depression Assessment

Depression and suicidal ideation were assessed using a Spanish-language version of the Patient Health Questionnaire-9 (PHQ-9) [25, 26]. The PHQ-9 is a nine item depression screening tool that has been validated in this population [17, 27]. The questionnaire assesses 9 depressive symptoms on the 14 days prior to evaluation. The PHQ-9 score is calculated by assigning a score of 0–3 to the response categories "not at all" "several days" "more than half the days" and "nearly every day". Suicidal ideation was assessed based on the PHQ-9 question inquiring as to patients having "thoughts that you would be better off dead or of hurting yourself in some way". Participants who responded to this question with "several days" "more than half the days" and "nearly every day" were categorized as affirmative for suicidal ideation. The question asking about suicidal ideation was not considered in the total score for depression. The first 8 questions (PHQ-8) were used to calculate a depression score. Participants were categorized as 'yes' for depression with a PHQ-8 score 10, similar to the cutoff for the PHQ-9. The use of the PHQ-8 depression questionnaire has been demonstrated to minimally influence overall scale performance, mean scores or diagnostic cut points as compared with use of PHQ-9 [28, 29].

Other Covariates

All subjects participated in structured interviews that included a questionnaire with information about sociodemographic, headache characteristics, and depression. Participants were also interviewed regarding sociodemographic characteristics. Participants' age was categorized as: 18–19, 20–29, 30–34, and 35 years old. Other covariates include education (6, 7–12, >12 years of education); pre-pregnancy self-reported body mass index (BMI) and early pregnancy measured BMI (<18.5, 18.5–24.9, 25–29.9, >30); ethnicity (Mestizo vs. others); marital status (married/living with partner vs. others); employment status (employed

vs. not employed); difficulty paying for the very basics (hard vs. not very hard); difficulty paying for medical care (hard vs. not very hard); parity (nulliparous vs. multiparous); planned pregnancy (yes vs. no); and gestational age at interview.

Statistical Analysis

Participants' demographic and reproductive characteristics were first examined. Continuous variables were presented as mean ± standard deviations (SD). Categorical variables were expressed as number (percent, %). Chi-square tests were used to evaluate differences in the distribution of categorical variables. Student's t-tests were used to evaluate differences in means. Multivariable logistic regression procedures were used to estimate odds ratios (OR) and 95% confidence intervals (95%CI) for suicidal ideation in relation to migraine diagnosis. Covariates were entered into each model individually, and adjusted and unadjusted ORs were compared to assess confounding. The final adjusted models included variables that were previously identified as potential confounders or altered the adjusted OR by at least 10%. Given that depression has been implicated as an important comorbid disorder with migraine, we repeated the analyses stratified by maternal depression status. We also explored the independent and joint effects of migraine and depression on the odds of suicidal ideation by categorizing participants into four groups based on the combination of depression and migraine status. The four categories examined were: (1) no migraine and no depression, (2) depression only, (3) migraine only, and (4) both migraine and depression. Pregnant women with no migraine and no depression were considered as the reference group and compared with women in the other three categories. All reported p-values are two sided with a statistical significance set at 0.05. Statistical analyses were performed using SPSS (IBM SPSS v22.0, Chicago, IL).

Results

The sociodemographic and reproductive characteristics of the study population are presented in Table 1. The average age of study participants was 28.2 years (SD=6.3); and the average gestational age at the interview was 9.2 weeks (SD=3.5). The majority of participants were Mestizos of mixed European and Amerindian descent (75.4%), married or living with a partner (81%), and multiparous (51.1%). Overall, compared to women without migraine, migraineurs were more likely to be unemployed, have difficulty paying for the basics and for medical care, have multiparous pregnancies, and do not identify as Mestizo (Table 1).

Suicidal ideation was endorsed by 16.0% of the cohort, and 26.2% of the cohort fulfilled criteria for depression. Participants with migraine or probable migraine (any migraine) had more than a two-fold increased odds of suicidal ideation (OR=2.17; 95%CI: 1.80–2.61) as compared with non-migraineurs (Table 2). After adjusting for confounders including age, marital status, difficulty paying for the basics, and difficulty paying for medical care, there was still an almost two-fold increase in suicidal ideation (OR=1.99; 95%CI: 1.64–2.41). Further adjustment for depression attenuated the association (OR=1.78; 95%CI: 1.46–2.17), although the association remained statistically significant. Separate analyses for women with migraine or probable migraine diagnosis also showed a consistent increased odds of suicidal ideation (probable migraine: OR=1.74; 95%CI: 1.39–2.19; migraine: OR=1.84; 95%CI:

1.41–2.42) when compared with non-migraineurs after adjusting for all of the above confounders. The magnitude and direction of associations remained similar after stratifying analyses by maternal depression status (Supplemental Table). For instance, after adjusting for confounders among participants with depression, migraineurs had a 1.75–fold increased odds of suicidal ideation as compared to non-migraineurs (OR=1.75;95%CI: 1.28–2.39). Among, participants without depression, migraineurs had a 1.80–fold increased odds of suicidal ideation (OR=1.80;95%CI: 1.40–2.32) as compared with non-migraineurs.

We next explored the independent and joint effect of migraine and depression on the odds of suicidal ideation (Table 3). In a fully adjusted model, women with depression and no migraine had a 2.44-fold increased odds of suicidal ideation (OR=2.44; 95%CI: 1.85-3.22) as compared with women who had no migraine and no depression (referent group). Those with migraine but no depression had a 1.84-fold increased odds of suicidal ideation (OR=1.84; 95%CI: 1.43–2.36) when compared with the referent group. Pregnant women with comorbid migraine and depression had a 4.14-fold increased odds of suicidal ideation (OR=4.14; 95%CI: 3.17–5.42) compared with those who had neither condition, although the interaction term did not reach statistical significance (p=0.706).

Discussion

In this study of pregnant women, those with migraine had increased odds of suicidal ideation even after controlling for depression. Specifically, after adjusting for confounders including depression, migraineurs had almost a 2-fold increased odds (OR=1.78; 95%CI: 1.46–2.17) of suicidal ideation compared with non- migraineurs. Women with both migraine and depression had a 4.14-fold increased odds (OR=4.14; 95%CI: 3.17–5.42) of suicidal ideation compared with those who had neither condition.

Given this is the first study to examine the relation between migraine and suicidal ideation in pregnancy, the results can be tentatively compared with studies that included men and non-pregnant women [30–32]. In a previous study among 1,007 members of a large Health Maintenance Organization in Michigan, Breslau *et al.* found a significant association between migraine and thoughts of committing suicide in patients with migraine [31]. Similarly, Fuller-Thomson and colleagues in their 2005 Canadian Community Health Survey (a general community-based population), found migraine was associated with increased odds of suicidal ideation in both men and women (men: OR=1.70; 95%CI: 1.55–1.96; women: OR=1.72; 95%CI: 1.59–1.86) although comorbid depression was not taken into account in this analysis [32]. In contrast to these studies, a tertiary care hospital-based study of Korean patients (N=238) reported that migraine patients had a 5-fold increased odds of suicidal ideation (OR=5.09; 95%CI: 1.17–22.1) compared with non-migraine patients; however after adjusting for comorbid depression and anxiety, the authors did not find a statistically significant association of suicidal ideation with migraine (OR=1.51; 95% CI: 0.31–7.50) [30].

Our study is the first to find evidence of an association between migraine and suicidal ideation among a cohort of pregnant women. The burden of migraine is particularly high among pregnant women, since migraine headaches are more prevalent among women of

childbearing age [6, 33]. The prevalence and frequency of headaches, including migraines, can also be altered during pregnancy and is thought to be influenced by hormonal changes across the menstrual cycle and during pregnancy [34]. In addition to migraine, additional risk factors make women in low- and middle-income countries particularly vulnerable to suicidal behaviors during pregnancy [35]. In our study, the association between migraine and suicidal ideation remained even when we adjusted for multiple confounders including depression.

There are plausible biological mechanisms for the association between migraine and suicidal ideation including shared genetic and neurochemical pathophysiological pathways [36]. Genetic and environmental risk factors have been identified for migraine headaches, depression, and suicidal behaviors [37, 38]. Studies have linked migraine, depression, and suicidal behaviors to polymorphic alleles of serotonin and dopamine, for example. A recent review of meta-analyses supports the association of serotonin transporter gene-linked polymorphic region (5-HTTLPR) with stress and depression symptoms [39], although this conclusion is controversial [40]. The distribution of polymorphism frequencies in 5-HTTLPR is significantly different among migraine and control patients [41]. Another study found 5-HTTLPR does not predispose individuals to develop migraines but may affect the frequency of attacks in migraine patients [42]. Studies have also found some evidence of an association between serotonin-related polymorphisms and suicidal behaviors, but the association is far from conclusive [43, 44]. Associations of serotonin transporter 5-HTTLPR with affective disorders may be mediated by fluctuations in estradiol and progesterone hormones [45]. Polymorphisms in the transcription initiation site of a serotonin transporter (5-HTT) show frequencies of the short allele are increased in migraine with aura patients but not in migraine without aura patients or controls, and this functional polymorphism is hypothesized to be related to migraine [46]. There is a significant association between alleles of the serotonin 5-HT2A receptor and both depression and suicide ideation [47]. Serotonin transporter function has been shown to be associated to suicidal behavior and depression [48]. Neural activity patterns also suggest differences in brain morphology in patients with a history of suicidal behaviors compared to patients without suicidal behavior [49, 50].

There is also evidence suggestive of genetic variations in the dopamine receptor gene associated with migraine, depression, and suicidal behaviors. One study showed increased incidence of migraine, depression, and anxiety disorders in individuals with the dopamine receptor DRD2 *Nco*I C allele in comparison to an DRD2 *Nco*I T allele in exon 6 [51]. Other studies, however, do not support this association [52]. In summary, suicidal behaviors have also been associated with variants in genes known to regulate both dopamine and serotonin metabolism [44]. Future studies are needed to more fully explore these associations and further elucidate hypothesized mechanisms.

The strengths of our study include a relatively large sample size, the use of well-trained interviewers, and rigorous statistical analytic approaches that included controls for confounding. However, there are some limitations that must be considered. First, because of the cross-sectional study design, we cannot be certain of the temporal relation between migraine and risk of suicidal ideation. Longitudinal studies with more detailed assessment of lifetime and recurrent episodes of suicidal ideation and suicidal behaviors with concomitant assessments of migraine and depression will enhance causal inferences in this area of

research. Second, migraine diagnosis was made using a well-established structured questionnaire based on ICHD-III criteria [24]. Use of structured interviews is the most feasible method of data collection for large scale epidemiologic studies. Additionally, this study is also subject to recall bias, as subjects are asked about past painful or traumatic experiences, including suicidal thoughts [53]. However the effect of this non-differential bias would most likely lead to an attenuation of the true association towards the null value. Lastly, our analysis did not distinguish between migraine with aura and migraine without aura. Migraine subtypes have been shown in previous studies to vary in the strength of their relationship with suicidal ideation, and this may also have attenuated the association reported in our study.

In conclusion, our study suggests that the risk of suicide ideation is increased among pregnant women with migraine. Pending replication, these findings have potential important clinical and public health implications. Specifically our findings suggest it may be important that clinicians treating pregnant women are aware of the comorbidity between migraine, depression, and suicidal behaviors and consider screening pregnant migraineurs for suicidal ideation [32, 54, 55].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. Current Pain and Headache Reports. 2011; 15:70–78. [PubMed: 21063918]

2. Lanteri-Minet M. Economic burden and costs of chronic migraine. Current Pain and Headache Reports. 2014; 18:385. [PubMed: 24338699]

3. Bigal ME, Lipton RB. The epidemiology, burden, and comorbidities of migraine. Neurologic Clinics. 2009; 27:321–334. [PubMed: 19289218]

4. Bigal ME, Liberman JN, Lipton RB. Age-dependent prevalence and clinical features of migraine. Neurology. 2006; 67:246–251. [PubMed: 16864816]

5. Finocchi C, Strada L. Sex-related differences in migraine. Neurological Sciences. 2014; 35(Suppl 1):207–213. [PubMed: 24867868]

6. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001; 41:646–657. [PubMed: 11554952]

7. Hamelsky SW, Lipton RB. Psychiatric comorbidity of migraine. Headache. 2006; 46:1327–1333. [PubMed: 17040330]

8. Samaan Z, Farmer A, Craddock N, Jones L, Korszun A, Owen M, McGuffin P. Migraine in recurrent depression: case-control study. British Journal of Psychiatry. 2009; 194:350–354. [PubMed: 19336787]

9. Breslau N, Lipton R, Stewart W, Schultz L, Welch K. Comorbidity of migraine and depression: investigating potential etiology and prognosis. Neurology. 2003; 60:1308–1312. [PubMed: 12707434]

10. World Health Organization. Millennium Development Goal 5 – improving maternal health. 2008.

11. Oates M. Perinatal psychiatric disorders: a leading cause of maternal morbidity and mortality. British Medical Bulletin. 2003; 67:219–229. [PubMed: 14711766]

12. Fuhr DC, Calvert C, Ronsmans C, Chandra PS, Sikander S, De Silva MJ, Patel V. Contribution of suicide and injuries to pregnancy-related mortality in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet Psychiatry. 2014; 1:213–225. [PubMed: 26360733]

13. Department of Reproductive Health and Research. World Health Organization. Mental health aspects of women's reproductive health: A global review of the literature. 2009.

14. Nock MK, Borges G, Bromet EJ, Cha CB, Kessler RC, Lee S. Suicide and suicidal behavior. Epidemiologic Reviews. 2008; 30:133–154. [PubMed: 18653727]

15. Han B, Compton WM, Gfroerer J, McKeon R. Prevalence and correlates of past 12-month suicide attempt among adults with past-year suicidal ideation in the United States. Journal of Clinical Psychiatry. 2015; 76:295–302. [PubMed: 25830449]

16. Oquendo MA, Baca-Garcia E, Mann JJ, Giner J. Issues for DSM-V: suicidal behavior as a separate diagnosis on a separate axis. American Journal of Psychiatry. 2008; 165:1383–1384. [PubMed: 18981069]

17. Zhong QY, Gelaye B, Rondon MB, Sanchez SE, Simon GE, Henderson DC, Barrios YV, Sanchez PM, Williams MA. Using the Patient Health Questionnaire (PHQ-9) and the Edinburgh Postnatal Depression Scale (EPDS) to assess suicidal ideation among pregnant women in Lima, Peru. Archives of Women's Mental Health. 2015; 18:783–792.

18. Gavin AR, Tabb KM, Melville JL, Guo Y, Katon W. Prevalence and correlates of suicidal ideation during pregnancy. Archives of Women's Mental Health. 2011; 14:239–246.

19. 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]

20. Barrios YV, Sanchez SE, Nicolaidis C, Garcia PJ, Gelaye B, Zhong Q, Williams MA. Childhood abuse and early menarche among Peruvian women. Journal of Adolescent Health. 2015; 56:197–202. [PubMed: 25620302]

21. Barrios YV, Gelaye B, Zhong Q, Nicolaidis C, Rondon MB, Garcia PJ, Sanchez PA, Sanchez SE, Williams MA. Association of childhood physical and sexual abuse with intimate partner violence, poor general health and depressive symptoms among pregnant women. PLoS One. 2015; 10:e0116609. [PubMed: 25635902]

22. Fung J, Gelaye B, Zhong QY, Rondon MB, Sanchez SE, Barrios YV, Hevner K, Qiu C, Williams MA. Association of decreased serum brain-derived neurotrophic factor (BDNF) concentrations in early pregnancy with antepartum depression. BMC Psychiatry. 2015; 15:43. [PubMed: 25886523]

23. Gelaye B, Barrios YV, Zhong QY, Rondon MB, Borba CP, Sanchez SE, Henderson DC, Williams MA. Association of poor subjective sleep quality with suicidal ideation among pregnant Peruvian women. General Hospital Psychiatry. 2015; 37:441–447. [PubMed: 25983188]

24. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33:629–808. [PubMed: 23771276]

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

26. Wulsin L, Somoza E, Heck J. The feasibility of using the Spanish PHQ-9 to screen for depression in primary care in Honduras. Primary Care Companion to the Journal of Clinical Psychiatry. 2002; 4:191–195.

27. Zhong Q, Gelaye B, Fann JR, Sanchez SE, Williams MA. Cross-cultural validity of the Spanish version of PHQ-9 among pregnant Peruvian women: a Rasch item response theory analysis. Journal of Affective Disorders. 2014; 158:148–153. [PubMed: 24655779]

28. Kroenke K, Spitzer RL, Williams JB, Lowe B. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. General Hospital Psychiatry. 2010; 32:345–359. [PubMed: 20633738]

29. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. Journal of Affective Disorders. 2009; 114:163–173. [PubMed: 18752852]

30. Kim SY, Park SP. Suicidal ideation and risk factors in Korean migraine patients. Journal of Clinical Neuroscience. 2014; 21:1699–1704. [PubMed: 24998861]

31. Breslau N. Migraine, suicidal ideation, and suicide attempts. Neurology. 1992; 42:392–395. [PubMed: 1736172]

32. 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

33. 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]

34. Pearce CF, Hansen WF. Headache and neurological disease in pregnancy. Clinical Obstetrics and Gynecology. 2012; 55:810–828. [PubMed: 22828113]

35. Gentile S. Suicidal mothers. Journal of Injury and Violence Research. 2011; 3:90–97. [PubMed: 21498972]

36. Hesdorffer DC, Lú vígsson P, Hauser WA, Ólafsson E, Kjartansson Ó. Co-occurrence of major depression or suicide attempt with migraine with aura and risk for unprovoked seizure. Epilepsy Research. 2007; 75:220–223. [PubMed: 17572070]

37. Montagna P. Molecular genetics of migraine headaches: a review. Cephalalgia. 2000; 20:3–14. [PubMed: 10817441]

38. Mandelli L, Serretti A. Gene environment interaction studies in depression and suicidal behavior: an update. Neuroscience & Biobehavioral Reviews. 2013; 37:2375–2397. [PubMed: 23886513]

39. Wankerl MWS, Otte C. Current developments and controversies: does the serotonin transporter gene-linked polymorphic region (5-HTTLPR) modulate the association between stress and depression? Current Opinion in Psychiatry. 2010; 23:582–587. [PubMed: 20881788]

40. Jin CXW, Yuan J, Wang G, Cheng Z. Meta-analysis of association between the -1438A/G (rs6311) polymorphism of the serotonin 2A receptor gene and major depressive disorder. Neurological research. 2013; 35:7–14. [PubMed: 23317793]

41. Borroni B, Brambilla C, Liberini P, Rao R, Archetti S, Gipponi S, Volta GD, Padovani A. Functional serotonin 5-HTTLPR polymorphism is a risk factor for migraine with aura. Journal of Headache and Pain. 2005; 6:182–184. [PubMed: 16362658]

42. Kotani KST, Shimomura F, Ikawa S, Nanba E. A polymorphism in the serotonin transporter gene regulatory region and frequency of migraine attacks. Headache. 2002; 42:893–895. [PubMed: 12390616]

43. McGuffin P, Marušic A, Farmer A. What can psychiatric genetics offer suicidology? Crisis. 2001; 22:61–65. [PubMed: 11727895]

44. Roy A. Genetic and biologic risk factors for suicide in depressive disorders. Psychiatric Quarterly. 1993; 64:345–358. [PubMed: 8234546]

45. Michopoulos V, Berga SL, Wilson ME. Estradiol and progesterone modify the effects of the serotonin reuptake transporter polymorphism on serotonergic responsivity to citalopram. Experimental and Clinical Psychopharmacology. 2011; 19:401–408. [PubMed: 21843009]

46. Marziniak MMR, Schmitt A, Lesch KP, Sommer C. A functional serotonin transporter gene polymorphism is associated with migraine with aura. Neurology. 2005; 64:157–159. [PubMed: 15642926]

47. Du LBD, Lapierre YD, Ravindran AV, Hrdina PD. Association of polymorphism of serotonin 2A receptor gene with suicidal ideation in major depressive disorder. American Journal of Medical Genetics (Neuropsychiatric Genetics). 2000; 96:56–60. [PubMed: 10686553]

48. Purselle DC, Nemeroff CB. Serotonin transporter: a potential substrate in the biology of suicide. Neuropsychopharmacology. 2003; 28:613–619. [PubMed: 12655305]

49. Desmyter S, van Heeringen C, Audenaert K. Structural and functional neuroimaging studies of the suicidal brain. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2011; 35:796–808. [PubMed: 21216267]

50. Jollant F, Lawrence NS, Giampietro V, Brammer MJ, Fullana MA, Drapier D, Courtet P, Phillips ML. Orbitofrontal cortex response to angry faces in men with histories of suicide attempts. American Journal of Psychiatry. 2008; 165:740–748. [PubMed: 18346998]

51. Peroutka SJPS, Wilhoit TL, Jones KW. Comorbid migraine with aura, anxiety, and depression is associated with dopamine D2 receptor (DRD2) NcoI alleles. Molecular medicine (Cambridge, Mass). 1998; 4:14–21.

52. Rebaudengo N, Rainero I, Parziale A, Rosina F, Pavanelli E, Rubino E, Mazza C, Ostacoli L, Furlan PM. Lack of interaction between a polymorphism in the dopamine D2 receptor gene and the clinical features of migraine. Cephalalgia. 2004; 24:503–507. [PubMed: 15154861]

53. Tietjen GE, Peterlin BL. Childhood abuse and migraine: epidemiology, sex differences, and potential mechanisms. Headache. 2011; 51:869–879. [PubMed: 21631473]

54. Fuller-Thomson E, Hamelin GP, Granger SJ. Suicidal ideation in a population-based sample of adolescents: implications for family medicine practice. ISRN Family Medicine. 2013; 2013:282378. [PubMed: 24967322]

55. Park SP, Seo JG, Lee WK. Osmophobia and allodynia are critical factors for suicidality in patients with migraine. Journal of Headache and Pain. 2015; 16:529. [PubMed: 25968102]

Table 1

Characteristics of the study population according to migraine status (N = 3,323)

Characteristics	All participants (N = 3,323)		No migraine (N = 2,200)		Probable migraine (N = 716)		Migraine (N = 407)		P-value
	n	%	n	%	n	%	n	%	
Age (years) [a]	28.19 ± 6.30		28.35 ± 6.29		27.82 ± 6.34		27.92 ± 6.28		0.099
Age (years)									
18–19	172	5.2	114	5.2	38	5.3	20	4.9	0.43
20–29	1848	55.6	1196	54.4	417	58.2	235	57.7	
30–34	700	21.1	477	21.7	135	18.9	88	21.6	
35	603	18.1	413	18.8	126	17.6	64	15.7	
Education (years)									
6	145	4.4	92	4.2	32	4.5	21	5.2	0.135
7–12	1806	54.5	1180	53.7	416	58.3	210	51.9	
>12	1363	41.1	924	42.1	265	37.2	174	43.0	
Pre-pregnancy self-reported BMI									
<18.5 kg/m^2	33	1.2	19	1.0	11	1.8	3	0.9	0.488
18.5–24.9	1471	53.1	985	54.2	307	50.9	179	51.1	
25–29.9	962	34.7	613	33.7	220	36.5	129	36.9	
>30	305	11.0	201	11.1	65	10.8	39	11.1	
Early pregnancy measured BMI									
<18.5 kg/m^2	63	1.9	30	1.4	27	3.8	6	1.5	**0.001**
18.5–24.9	1582	48.2	1053	48.5	322	45.5	207	51.4	
25–29.9	1210	36.9	792	36.5	277	39.1	141	35.0	
>30	428	13.0	297	13.7	82	11.6	49	12.2	
Mestizo ethnicity	2501	75.4	1650	75.1	576	80.4	275	67.7	**<0.001**
Married/living with a partner	2679	81.0	1764	80.6	584	81.9	331	81.5	0.705
Employed	1525	45.9	1069	48.6	286	39.9	170	41.8	**<0.001**
Difficulty paying for basics									
Hard	1649	49.7	1016	46.2	397	55.4	236	58.0	**<0.001**
Not very hard	1672	50.3	1182	53.8	319	44.6	171	42.0	
Difficulty paying for medical care									

Characteristics	All participants (N = 3,323)		No migraine (N = 2,200)		Probable migraine (N = 716)		Migraine (N = 407)		P-value
	n	%	n	%	n	%	n	%	
Hard	1760	53.1	1067	48.7	438	61.2	255	62.8	**<0.001**
Not very hard	1554	46.9	1125	51.3	278	38.8	151	37.2	
Nulliparous	1621	48.9	1103	50.3	340	47.6	178	43.8	**0.040**
Planned pregnancy	1390	42.1	948	43.3	291	40.9	151	37.4	0.063
Gestational age at interview [a]	9.24 ± 3.46		9.25 ± 3.47		9.27 ± 3.41		9.18 ± 3.45		0.903
Thoughts that you would be better off dead or of hurting yourself in some way									
No	2790	84.0	1929	87.7	558	77.9	303	74.4	**<0.001**
Yes	533	16.0	271	12.3	158	22.1	104	25.6	
Depression (PHQ-8)	865	26.2	472	21.6	213	30.0	180	44.8	**<0.001**

Due to missing data, percentages may not add up to 100%.

[a]mean ± SD (standard deviation): How many weeks pregnant were you during your first prenatal care visit?

[b]For continuous variables, *P*-value was calculated using the one-way ANOVA; for categorical variables, *P*-value was calculated using the Chi-square test.

Table 2

Association of migraine with suicidal ideation during pregnancy (N=3,323)

Migraine	No suicidal ideation (N = 2,790)		Suicidal ideation (N = 533)				
	n	%	n	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI) [a]	Adjusted OR (95% CI) [b]
No migraine	1929	69.1	271	50.8	Reference	Reference	Reference
Any migraine	861	30.9	262	49.2	2.17 (1.80–2.61)	1.99 (1.64–2.41)	1.78 (1.46–2.17)
Types of migraine							
No migraine	1929	69.1	271	50.8	Reference	Reference	Reference
Probable migraine	558	20.0	158	29.6	2.02 (1.62–2.51)	1.88 (1.50–2.34)	1.74 (1.39–2.19)
Migraine	303	10.9	104	19.5	2.44 (1.89–3.16)	2.20 (1.69–2.86)	1.84 (1.41–2.42)

Abbreviations: OR, odds ratio; CI, confidence interval

[a]Adjusted for age, marital status, difficulty paying for the very basics, difficulty paying for medical care

[b]Adjusted for age, marital status, difficulty paying for the very basics, difficulty paying for medical care, and depression

Table 3

Independent and joint associations of migraine and depression with odds of suicidal ideation

Migraine and Depression Status	No Suicidal Ideation (N = 2,773)		Suicidal Ideation (N = 524)			
	n	%	n	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI) [a]
(−) Migraine, (−) Depression	1544	55.7	168	32.1	Reference	Reference
(−) Migraine, (+) Depression	373	13.5	99	18.9	2.44 (1.86–3.21)	2.44 (1.85–3.22)
(+) Migraine, (−) Depression	593	21.4	127	24.2	1.97 (1.53–2.53)	1.84 (1.43–2.36)
(+) Migraine, (+) Depression	263	9.5	130	24.8	4.54 (3.49–5.91)	4.14 (3.17–5.42)
P value for interaction term					0.783	0.706

Abbreviations: OR, odds ratio; CI, confidence interval

[a] Adjusted for age, marital status, difficulty paying for the very basics, and difficulty paying for medical care