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The Association Between Parental Migraine and Infant Colic: A Cross-Sectional, Web-Based, U.S. Survey Study

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Background.—Infant colic, or excessive crying in an otherwise healthy infant, is common, although the cause(s) are not known. This study aimed to determine whether parental migraine is associated with infant colic.

Methods.—This was a cross-sectional online survey study of biological parents of 4-8 week olds in the United States during February and March 2017 and October 2017-April 2018. Parents self-reported information about their and their infant's health using validated instruments wherever possible. Parents were recruited using social media advertisements and completed the survey online. Migraine was identified with a validated screener using modified International Classification of Headache Disorders 3rd edition criteria. Parental depression and anxiety were screened with the Patient Health Questionnaire-2 (PHQ-2) and Generalized Anxiety Disorder Scale-2 (GAD-2). Parental seasonal allergies and asthma were assessed by self-report. Infant colic was determined based on parental response to the question, "Has your baby cried for at least 3 hours on at least 3 days in the last week?"

Results.—A total of 1,715 surveys were completed over 2 recruitment periods; 1,419 formed the analysis set. Eight hundred twenty-seven were completed by biological mothers and 592 by biological fathers. Mean (SD) maternal age: 28.9 (5.1) years; 33.5% had migraine/probable migraine. Maternal migraine was associated with increased odds of infant colic: OR 1.7 (1.3-2.4). Among mothers with migraine, headache frequency ≥15 days/month was associated with higher risk of infant colic (OR 2.5 (1.2-5.3)); and anxiety was borderline associated (OR 1.7 (1.0-2.9)). Mean (SD) paternal age was 31.6 (4.5) years; 20.8% had migraine/probable migraine. Paternal migraine was not associated with infant colic: OR 1.0 (0.7-1.5). Fathers with depression (OR 2.4 (1.4-4.3)) or anxiety (OR 1.7 (1.1-2.7)) were more likely to have a baby with colic but having a girl infant was protective: (OR 0.7 (0.5-0.97)).

Conclusions.—Mothers with migraine are more likely to have a baby with colic, while fathers with migraine are not. Further research is needed to determine the mechanisms underlying these findings. In the meantime, clinicians may wish to counsel parents with a maternal history of migraine about the increased possibility of having a colicky infant and provide resources and education about infant crying.

Key words: migraine, infant colic, depression, anxiety

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INTRODUCTION

Infant colic, or excessive crying in an otherwise healthy and well-fed infant, affects approximately 5-19% of babies.[1-3] Infant crying peaks at age 5-6 weeks (corrected for gestational age at birth) and generally decreases by age 3-4 months.[4] Colic is likely an amplified version of this developmental crying pattern. While definitions of infant colic vary, Wessel's criteria[5] are commonly used and are the criteria used in the International Classification of Headache Disorders (ICHD) 3rd edition (appendix):[6] crying for at least 3 hours a day, at least 3 days a week, for at least 3 weeks.

Despite decades of research, we still do not understand the cause, or causes, of infant colic. Previous research has suggested that maternal anxiety and depression[7-9] are associated with infant colic, as well as paternal depression.[10] A previous study by our group demonstrated that mothers with migraine were more than twice as likely to have a baby with colic,[2] and another study similarly found an association between maternal migraine and infant colic.[11] To date, the results of treatment trials for infant colic have not necessarily helped to inform our understanding of its etiology. A randomized placebo-controlled trial of simethicone,[12] a treatment aimed at reducing intestinal gas, was negative. Based on the hypothesis that the gut microbiome plays a role in colic there have been several treatment trials of specific probiotic strains though results have been variable.[13-16]

The age-related pattern to infant crying suggests it may be a neurodevelopmental process. In addition, multiple retrospective studies have demonstrated an association between infant colic and the development of migraine later in childhood or adolescence.[17-19] A prospective cohort study in Finland demonstrated that infants with a history of colic were more likely to develop migraine without aura by age 18.[20] We also previously demonstrated an association between maternal migraine and infant colic,[2] suggesting infant colic might be an early life manifestation of migraine genetics.

Migraine is a neurologic disease characterized by increased sensitivity to stimuli—such as lights, sounds, and touch—both during and between attacks.[6,21-23] Migraine is thought to be largely genetic in that there is typically a family history.[24] One hypothesis is that infants who inherit a genetic susceptibility toward migraine have brains that are more sensitive to the stimuli they encounter once outside of the womb.[25] Given the observations to date indicating an association between migraine and infant colic, in this study we aimed to determine whether the previously observed association between maternal migraine and infant colic could be replicated in a larger U.S. sample and to explore the relationship between paternal migraine and infant colic. We hypothesized that:

1. mothers with migraine would be more likely to have a baby with colic—and that this association would hold after adjusting for other factors known to be associated both with migraine and infant colic, eg, parental depression and/or anxiety;[7,8,10,26,27]
2. mothers with migraine with aura would be less likely than those without aura to have an infant

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with colic, given that in the Finnish prospective adolescent cohort study colic was associated with development of migraine without aura, but not migraine with aura, by age 18;[20]
3. there would be a "dose-response" in that mothers with higher migraine frequency would be more likely to have an infant with colic; and
4. the above would also hold true for fathers.

METHODS

Consents and Approvals.—This study was approved by the UCSF internal review board (#16-21184) and parents provided their consent to participate.

Study Population.—We conducted a cross-sectional study of parents in the United States via an online survey. Parents had infants 4-8 weeks of age (ie, 44-48 weeks post-conceptional age). This target infant age range was chosen because infant crying peaks in this age window.[4,28]

Infant Variables.—*Demographics.*—To determine infants' developmental age, parents were asked to provide their baby's due date as well as their baby's actual date of birth. To be included in the analysis the infant had to be 4-8 weeks out from their due date at the time the survey was completed. Parents were also asked the sex of their infant, and whether or not this was their first born.

Colic Status.—Colic status was treated as a dichotomous variable and was determined based on parental response to: "Has your baby cried for at least 3 hours on at least 3 days in the last week?" This methodology, or variants of it, has been used previously to determine the presence of infant colic.[2,3]

Parental Variables.—*Sociodemographic Data.*—Sociodemographic data including relationship to the infant (ie, mother vs father, biological or adoptive parent), age, ethnicity, race, highest level of education completed (as a surrogate for household income[29]), marital status, zip code/state, number of children and the question, "Did you cry a lot as a baby yourself?" were obtained via self-report. Given the genetic nature of our hypotheses, we restricted our analyses to biological parents.

Determination of Migraine Status.—Parental migraine status was queried in several ways: (1) parent's self-report of having migraine; (2) parent's self-report of having received a physician diagnosis of migraine; and (3) The American Migraine Study/American Migraine Prevalence and Prevention Study (AMS/AMPP) diagnostic module[30] was used to assess whether the parent met modified International Classification of Headache Disorders (ICHD) 3rd edition criteria for migraine or probable migraine. This validated module assesses lifetime recall of symptoms associated with the respondent's most severe type of headache (eg, unilateral, pulsating, moderate/severe pain intensity, routine activity exacerbation of headache pain, nausea, phonophobia, and photophobia) which are the 7 ICHD criteria for migraine.[6] There are four response options for each symptom: never, rarely, less than half the time and half the time or more. This diagnostic module has been demonstrated to have a sensitivity of 100% and specificity of 82% for the diagnosis of migraine.[30] The module was validated based upon ICHD-2 criteria; however, no significant changes occurred between ICHD-2 and ICHD-3 that are related to the criteria used in this study. In terms of modifications, the criteria used for migraine are the same as outlined in ICHD-3 with the exception of Criterion A (a lifetime history of ≥5 migraine attacks).[6]

In addition, the survey contained questions about:

1. Lifetime visual aura with migraine status—Respondents were asked: "Have you ever seen things like spots, stars, lines, flashing lights, zigzag lines, or 'heat waves' around the time of your most severe type of headache?," which was written to assess visual aura with migraine as part of the aura module in the AMPP Study, and, if so, "How long do these changes in your vision last on average? (minutes)." Given that the majority of people who experience other types of aura also experience visual aura,[31] for the purposes of this study those who answered "yes" to the first question and who indicated that their symptoms last for ≥5 minutes (the minimum duration required in ICHD-3 for aura criteria) were considered to have aura.
2. Headache frequency (in days per month) was assessed with the headache frequency question from the migraine disability assessment scale (MIDAS[32])

"On how many days in the last month (30 days) did you have a headache (if a headache lasted more than 1 day, count each day)?" Frequency was examined both as a continuous and as a dichotomous variable. As headache occurring on ≥15 days per month is the cutpoint for "chronic migraine" in ICHD-3,[6] this was used as the cutpoint for dichotomous analysis in this study.

Comorbidities.—To be able to adjust for potential confounding, several comorbidities known to be associated both with infant colic and with migraine in adults were assessed by self-report.[1,7,8,10,27,33-37]

For seasonal allergies and asthma, parents were asked: (1) whether they had the condition and (2) whether they had ever been diagnosed by a physician with the condition.

To measure parental depression and anxiety, we used the Patient Health Questionnaire 2 (PHQ-2) and Generalized Anxiety Disorder Scale 2 (GAD-2) screeners. These consist of the first 2 items of the PHQ-9 and GAD-7 respectively and constitute the two core DSM-5 items for major depressive disorder and generalized anxiety disorder, respectively. Each has a score ranging from 0 to 6, with a validated screening cutpoint of ≥3.[38]

Recruitment and Power Calculation.—Parents were recruited online using social media advertisements (eg, Facebook®). The advertisements intentionally did not mention migraine, headaches, colic, or infant crying.

We aimed to recruit approximately 1,000 participants in order to have adequate power to determine whether there is an association between (1) maternal migraine and infant colic; (2) paternal migraine and infant colic; and (3) to be able to adjust for aspects such as aura status and migraine/headache day frequency. There was not a formal power analysis for this portion of the study. However, after recruiting the first sample, we found that the overwhelming majority of respondents were mothers. We then collected a second sample using social media advertisements that targeted fathers. For this second collection, we assumed that approximately 10% of father respondents would have migraine, and thus we would need 625 fathers to have 80% power and 95% confidence to detect a difference of 5% or greater in the likelihood of a baby having colic based on paternal migraine status. As we had also observed in the first sample that some respondents had infants outside of the target age range, we aimed to recruit 700 fathers in order to have analyzable data from 625.

Statistical Analysis.—Mann-Whitney and chi-square tests were used for continuous and categorical variables, respectively. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using logistic regression. Analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Pre-specified analyses included examining for associations between parental migraine and infant colic, and for comorbidities that are associated with both conditions (asthma, allergies, depression, and anxiety), as well as migraine features such as aura and headache day frequency and parental history of excessive crying. *Post-hoc* analyses examined whether birth order and infant sex were predictors of colic both in the overall sample and within the subsamples with parental migraine.

RESULTS

Maternal Data.—One thousand and ten surveys (n = 1,010) were completed during February and March 2017 by respondents living in 48 states. Of these, 7 surveys were excluded because they did not include a response to the question about infant colic, and an additional 108 were excluded for not being completed in the 4-8 week post due date age range, leaving 895 remaining. Eight hundred twenty-seven (827) were completed by the biological mother; the other 68 were completed by either an adoptive parent (n = 6), the biological father (n = 5), or the relationship was not specified (n = 57).

The maternal analyses are based on the 827 biological mothers' responses; 212 (25.6%) of their infants had colic. Babies with colic did not differ from those without colic in age: 5.7 (1.0) vs 5.8 (1.1) weeks (mean (SD), P = .44)), sex: 48.1% girls vs 48.7% (P = .88), or proportion of first borns: 60.8% vs 60.0% (P = .84).

Demographic and clinical information for the 827 biological mothers is detailed in Table 1. Mean (SD) maternal age was 28.9 (5.1) years. The proportion of biological mothers who met modified ICHD-3 criteria for migraine was 34.6% (n = 286), and 36.3% (n = 300) had migraine or probable migraine by modified

Table 1.—Clinical and Sociodemographic Information for the 827 Biological Mothers, With Test Comparisons for Selected Comorbidities

	Mothers Without Migraine (*n* = 527)	Mothers With Migraine/ Probable Migraine (*n* = 300)	All Mothers (*n* = 827)
Mean age (SD), years, (min-max)	29.1 (5.0), (18-40); (*n* = 525)	28.6 (5.2), (15-40); (*n* = 299)	28.9 (5.1), (15-40); (*n* = 824)
Total number of children, including current infant, (median) (min-max)	1 (1-8), (*n* = 517)	1 (1-8), (*n* = 299)	1 (1-8), (*n* = 816)
Current infant is a girl	50% (*n* = 263/526)	**46%** (*n* = 138/300)	48.6% (*n* = 401/826)
Self-report of excessive crying as an infant	26.2% (*n* = 90/343)	**32.5%** (*n* = 64/197)	28.5% (*n* = 154/540)
Depression (PHQ-2 ≥3)*	**7.5%** (*n* = 38/506)	**15.3%** (*n* = 45/295)	10.4% (*n* = 83/801)
Anxiety (GAD-2 ≥3)*	**19.3%** (*n* = 98/507)	**27.7%** (*n* = 82/296)	22.4% (*n* = 180/803)
Seasonal allergies (self-report)*	**41%** (*n* = 216/527)	**64%** (*n* = 192/300)	49.3% (*n* = 408/827)
Asthma (self-report)*	**11.4%** (*n* = 60/526)	**18.1%** (*n* = 54/299)	13.8% (*n* = 114/825)
Ethnicity: *n* (%)			
Hispanic	58 (11.0%)	24 (8.0%)	82 (9.9%)
Non-Hispanic	469 (89.0%)	275 (92.0%)	744 (90.1%)
Total	527	299	826
Race: *n* (%)			
White	461 (87.8%)	267 (89.3%)	728 (88.3%)
Black/African American	26 (5.0%)	11 (3.7%)	37 (4.5%)
Native American	5 (1.0%)	6 (2.0%)	11 (1.3%)
Asian	14 (2.7%)	8 (2.7%)	22 (2.7%)
Pacific Islander	1 (0.2%)	2 (0.7%)	3 (0.4%)
Other	18 (3.4%)	5 (1.7%)	23 (2.8%)
Total	525	299	824
Highest education level: *n* (%)			
8 grades or less	1 (0.2%)	1 (0.3%)	2 (0.2%)
Some high school	9 (1.7%)	8 (2.7%)	17 (2.1%)
High school graduate/GED	53 (10.1%)	38 (12.7%)	91 (11.0%)
Some college or technical school	179 (34.0%)	117 (39%)	296 (35.8%)
College graduate (bachelor's degree)	167 (31.7%)	87 (29.0%)	254 (30.7%)
Graduate degree**	**118** (22.4%)	**49** (16.3%)	**167** (20.2%)
Total	527	300	827
Marital status: *n* (%)			
Single	58 (11.0%)	33 (11.0%)	91 (11.0%)
Married	410 (77.8%)	222 (74.2%)	632 (76.5%)
Separated/divorced	6 (1.1%)	3 (1.0%)	9 (1.1%)
Live with domestic partner	53 (10.1%)	41 (13.7%)	94 (11.4%)
Total	527	299	826

*$P < .01$.
**$P = .04$.
Migraine/probable migraine definition used was meeting modified ICHD-3 criteria at the time of the survey by respondent self-response to the validated American Migraine Study/American Migraine Prevalence and Prevention Study (AMS/AMPP) diagnostic module.[30]
SD = standard deviation.
Bold values are the analyses where the mothers with migraine differed from those without migraine.

ICHD-3 criteria. Mothers with migraine and mothers without migraine were similar demographically, except mothers with migraine were less likely to have a graduate degree: 16.3% vs 22.4%, $P = .04$. Mothers with migraine were more likely to have comorbidities known to be associated with migraine in adults, namely depression, anxiety, seasonal allergies, and asthma.

Predictors of Infant Colic among All Mothers (*n* = 827).—Maternal migraine was associated with increased odds of infant colic in all 4 ways that the association was tested; see Table 2.

Mothers with depression had increased odds of having a baby with colic. Maternal anxiety was associated with increased odds of infant colic, but this was not statistically significant. No other maternal

Table 2.—Associations Between Maternal and Baby-Related Characteristics and Infant Colic (*n* = 827 Biological Mothers and their Infants)

	Proportion of Infants With Colic Born to Mothers With vs Without the Predictor	*P* Value	OR (95% CI)
Predictor name (number in the analysis)			
Migraine (4 ways):			
Self-reported migraine (*n* = 825)	30.7% vs 23.2%	.02	**1.5 (1.1-2.0)†** **1.5 (1.1-2.1)‡**
Self-report of physician diagnosis of migraine (*n* = 630)	31.6% vs 22.6%	.02	**1.6 (1.1-2.3)†** **1.6 (1.1-2.4)‡**
Modified ICHD-3 criteria for migraine (*n* = 827)	33.2% vs 21.6%	<.01	**1.8 (1.3-2.5)†** **1.8 (1.3-2.5)‡**
Modified ICHD-3 criteria for migraine/probable migraine (*n* = 827)	32.3% vs 21.8%	<.01	**1.7 (1.3-2.4)†** **1.7 (1.2-2.4)‡**
Seasonal allergies (self-report), (*n* = 827)	25.5% vs 25.8%	.93	1.0 (0.7-1.4)
Asthma (self-report), (*n* = 825)	22.8% vs 26.2%	.45	0.8 (0.5-1.3)
Anxiety (GAD-2), (*n* = 803)	31.1% vs 24.2%	.06	1.4 (1.0-2.0)
Depression (PHQ-2), (*n* = 801)	38.6% vs 24.2%	<.01	**2.0 (1.2-3.2)†** **1.8 (1.1-2.9)§**
Mother having cried a lot as an infant themselves (*n* = 540)	24.7% vs 24.4%	.94	1.0 (0.7-1.6)
Infant is mother's first born (*n* = 816)	25.9% vs 25.2%	.84	1.0 (0.8-1.4)
Infant is a girl (*n* = 826)	25.4% vs 25.9%	.88	1.0 (0.7-1.3)

†Unadjusted.
‡Adjusted for maternal anxiety and depression.
§Adjusted for maternal migraine.
CI = confidence interval; OR = odds ratio.

comorbidities or infant characteristics were associated with infant colic (see Table 2). Adjusting for maternal depression and anxiety did not meaningfully change the magnitude of the observed associations between maternal migraine and infant colic (see Table 2).

Predictors of Infant Colic among Mothers With Migraine (*n* = 300). See Table 3.—Among mothers with modified ICHD-3 migraine/probable migraine, 32.3% of their infants had colic (*n* = 97/300). Mothers with migraine who experienced ≥15 headache days in the last month were more likely to have a baby with colic than those with fewer headache days per month: 52% (17/33) vs 30% (78/264), *P* = .01; OR 2.5 (1.2-5.3). There was a "dose-response" in that for every 10-day increase in maternal headache frequency, odds of having a baby with colic increased by 60% (OR 1.6 (1.1-2.4). Mothers with migraine with aura (41.3% *n* = 124/300) were not statistically more likely to have a baby with colic: 37% (46/124) vs 29% (51/176), *P* = .14.

Mothers with migraine who also had depression were numerically, but not statistically, more likely to have an infant with colic compared to those who did not have depression: 42% (19/45) vs 31% (78/250), *P* = .15, OR 1.6 (0.8-3.4). Mothers with migraine who also had anxiety were more likely to have a baby with colic: 42% (34/82) vs 29% (63/214) of those without comorbid anxiety, and this finding neared statistical significance: *P* = .05, OR 1.7 (1.0-2.9).

About two-thirds of mothers with migraine reported whether or not they had been colicky themselves as infants. Of these, 33% (21/64) of those who had been colicky themselves had a baby with colic vs 29% (39/133) of those who had not been, *P* = .62.

Mothers with migraine having their first child were not more likely to have a colicky baby: 34% (58/171) vs 31% (39/128), *P* = .53, *n* = 299, OR 1.2 (0.7-1.9). Infant sex was not associated with infant colic: 34% (47/138) of girls vs 31% (50/162) of boys born to mothers with migraine had colic, *P* = .56, *n* = 300, OR 1.2 (0.7-1.9).

Table 3.—Predictors of Infant Colic among Mothers (*n* = 300) and Fathers (*n* = 123) With Migraine/Probable Migraine

	Maternal Data	Paternal Data
	OR (95% CI)	OR (95% CI)
Predictor:		
Aura	1.5 (0.9-2.4) (*n* = 300)	0.8 (0.4-1.8) (*n* = 123)
Headache ≥15 days per month	**2.5 (1.2-5.3)** (*n* = 297)	0.9 (0.3-3.1) (*n* = 122)
For every 10 day increase in headache frequency	1.6 (1.1-2.4) (*n* = 297)	
Anxiety (GAD-2 ≥3)	1.7 (1.0-2.9) (*n* = 296)	1.5 (0.7-3.4) (*n* = 118)
Depression (PHQ-2 ≥3)	**1.6 (0.8-3.1)** (*n* = 295)	**2.6 (1.4-4.7)** (*n* = 118)
Seasonal allergies (self-report)	0.8 (0.5-1.3) (*n* = 300)	0.9 (0.4-1.9) (*n* = 123)
Asthma (self-report)	0.7 (0.4-1.3) (*n* = 299)	
Parental self-report of having cried a lot as an infant	1.2 (0.6-2.2) (*n* = 197)	1.5 (0.6-3.8) (*n* = 72)
First baby	1.2 (0.7-1.9) (*n* = 299)	1.6 (0.7-3.6) (*n* = 120)
Girl baby	1.2 (0.7-1.9) (*n* = 300)	**0.4 (0.2-0.9)** (*n* = 121)

Paternal Data.—In the second recruitment period, 705 surveys were completed between October 2017 and April 2018 by respondents living in 49 states and the District of Columbia. Of these, 78 surveys were not analyzed, as they were outside of the target infant age range and 2 surveys were also missing information on colic. Of the remaining 627 surveys, 587 were completed by biological fathers and had information on paternal headaches; 39 were missing information on paternal headaches and 1 was completed by the mother. To this group, we added the 5 surveys from the first round that were completed by biological fathers for a total cohort of 592 biological fathers.

One hundred ninety-three (32.6%) of the 592 infants had colic. Babies with colic were slightly younger than those without colic: 5.5 (1.1) vs 5.8 (1.1) weeks, (mean (SD)), $P \leq .01$)) and more likely to be male: 59.1% (114/193) boys vs 50.1% (200/399) ($P = .04$), but not more likely to be first borns: 66.3% (126/190) vs 68.0% (270/397) ($P = .68$).

Demographic and clinical information for the 592 biological fathers are detailed in Table 4. Mean(SD) paternal age was 31.6 (4.5) years. The proportion of fathers with migraine was 15.9% (94/592) by self-report, 10.8% (49/455) by self-report of a physician diagnosis, and 19.5% (115/592) by modified ICHD-3 criteria; 20.8% (123/592) had migraine or probable migraine by modified ICHD-3 criteria. Fathers with migraine were more likely to have anxiety, depression, and seasonal allergies. They were also more likely to have cried excessively as infants. See Table 4.

Predictors of Infant Colic among All Fathers (*n* = 592).—Unlike with mothers, paternal migraine was not associated with infant colic, regardless of the migraine definition used (see Table 5). Paternal anxiety and depression were associated with increased odds of infant colic, and having a girl baby was protective (see Table 5).

Predictors of Infant Colic among the Fathers With Migraine (*n* = 123). See Table 3.—Among fathers who met modified ICHD-3 criteria for migraine/probable migraine, those who experienced ≥15 headache days in the last month were not more likely to have a baby with colic than those with fewer headache days per month: 31% (4/13) vs 33% (36/109), $P = .87$; OR 0.9 (0.3-3.1). There also was not a "dose-response." For every 10-day increase in paternal headache frequency, odds of having a baby with colic did not increase: OR 1.0 (0.6-1.9).

Fathers with migraine with aura (43%, *n* = 53/123) were not less likely to have a baby with colic than those with migraine without aura: 30% (16/53) vs 34% (24/70), $P = .63$; OR 0.8 (0.4-1.8).

Among fathers with migraine, those who also had anxiety were numerically, but not statistically, more likely to have a baby with colic: 39% (15/39) vs 29% (23/79), $P = .31$, OR 1.5 (0.7-3.4). Similarly, fathers with migraine and depression were also numerically, but

Table 4.—Clinical and Sociodemographic Information for the 592 Biological Fathers, With Test Comparisons for Selected Comorbidities

	Fathers Without Migraine (*n* = 469)	Fathers With Migraine/ Probable Migraine (*n* = 123)	All Fathers (*n* = 592)
Mean age (SD), years, (min-max)	31.7 (4.5), (16-44) (*n* = 465)	31.3 (4.8), (20-40) (*n* = 123)	31.6 (4.5), (16-44) (*n* = 588)
Total number of children, including current infant (median), (min-max))	1 (1-7) (*n* = 465)	1 (1-5) (*n* = 122)	1 (1-7) (*n* = 587)
Current infant is a girl	47.1% (*n* = 221/469)	46.3% (*n* = 57/123)	46.8% (*n* = 275/592)
Self-report of excessive crying as an infant:**	**25.5%** (*n* = 68/267)	**38.9%** (*n* = 28/72)	**28.3%** (*n* = 98/339)
Depression (PHQ-2 ≥3)*	**5.7%** (*n* = 26/458)	**22.0%** (*n* = 26/118)	**9.0%** (*n* = 52/576)
Anxiety (GAD-2 ≥3)*	**10.3%** (*n* = 47/459)	**33.1%** (*n* = 39/118)	**14.9%** (*n* = 86/577)
Seasonal allergies (self-report)*	**39.4%** (*n* = 185/469)	**65.0%** (*n* = 80/123)	**44.8%** (*n* = 265/592)
Asthma (self-report)	**12.4%** (*n* = 58/469)	**17.2%** (*n* = 21/122)	13.4% (*n* = 79/591)
Ethnicity: *n* (%)			
Hispanic	49 (10.5%)	7 (5.7%)	56 (9.5%)
Non-Hispanic	419 (89.5%)	116 (94.3%)	535 (90.5%)
Total	468	123	591
Race: *n* (%)			
White	364 (77.8%)	110 (89.4%)	474 (80.2%)
Black/African American	26 (5.6%)	3 (2.4%)	29 (4.9%)
Native American	3 (0.6%)	0 (0.0%)	3 (0.5%)
Asian	46 (9.8%)	6 (4.9%)	52 (8.8%)
Pacific Islander	6 (1.3%)	1 (0.8%)	7 (1.2%)
Other	23 (4.9%)	3 (2.4%)	26 (4.4%)
Total	468	123	591
Highest education level: *n* (%)			
8 grades or less	1 (0.2%)	0 (0.0%)	1 (0.2%)
Some high school	5 (1.1%)	0 (0.0%)	5 (0.8%)
High school graduate/GED	32 (6.8%)	17 (13.8%)	49 (8.3%)
Some college or technical school	119 (25.4%)	34 (27.6%)	153 (25.9%)
College graduate (bachelor's degree)	172 (36.8%)	45 (36.6%)	217 (36.7%)
Graduate degree	139 (29.7%)	27 (22.0%)	166 (28.1%)
Total	468	123	591
Marital status: *n* (%)			
Single	23 (4.9%)	7 (5.7%)	30 (5.1%)
Married	401 (86.1%)	107 (87.0%)	508 (86.2%)
Separated/Divorced	6 (1.3%)	0 (0.0%)	6 (1.0%)
Live with Domestic partner	36 (7.7%)	9 (7.3%)	45 (7.6%)
Total	466	123	589

*$P < .001$.
**$P = .03$.

not statistically, more likely to have babies with colic: 46% (12/26) vs 28% (26/92), $P = .09$, OR 2.2 (0.9-5.3).

Of the fathers with migraine who knew whether or not they had cried excessively as infants ($n = 72$), 43% (12/28) of those who had been colicky themselves had a baby with colic vs 34% (15/44) of those who had not been colicky themselves, $P = .45$. Fathers with migraine having their first child were not statistically more likely to have a colicky infant than those having a subsequent child: 36% (26/73) vs 26% (12/47), $P = .25$, OR 1.6 (0.7-3.6). However, fathers with migraine having a girl baby were less likely to have a colicky baby: 22% (12/55) girls had colic vs 41% (27/66) of boys, $P = .03$, OR 0.4 (0.2-0.9).

DISCUSSION

In our study, we found that mothers with migraine were more likely to have a baby with colic. The association was robust in that it held regardless of the way migraine status was assessed. Maternal

Table 5.—Associations Between Paternal and Baby-Related Characteristics and Infant Colic (*n* = 592 Biological Fathers and their Infants)

	Proportion of Infants With Colic Born to Fathers With vs Without the Predictor	*P* Value	OR (95% CI)
Predictor name (number in the analysis)			
Migraine (4 ways):			
Self-reported migraine (*n* = 592)	34.0% vs 32.3%	.75	1.1 (0.7-1.7)
Self-report of physician diagnosis of migraine (*n* = 456)	34.7% vs 31.7%	.67	1.2 (0.6-2.1)
Modified ICHD-3 criteria for migraine (*n* = 592)	33.0% vs 32.5%	.91	1.0 (0.7-1.6)
Modified ICHD-3 criteria for migraine/probable migraine (*n* = 592)	32.5% vs 32.7%	.98	1.0 (0.7-1.5)
Seasonal allergies (self-report) (*n* = 592)	32.5% vs 32.7%	.94	1.0 (0.7-1.4)
Asthma (self-report) (*n* = 591)	35.4% vs 32.2%	.57	1.2 (0.7-1.9)
Anxiety (GAD-2) (*n* = 577)	**43.0% vs 31.0%**	**.03**	**1.7 (1.1-2.7)**
Depression (PHQ-2) (*n* = 576)	**51.9% vs 30.9%**	**<.01**	**2.4 (1.4-4.3)**
Father having cried a lot as an infant themselves (self-report) (*n* = 339)	39.6% vs 32.5%	.22	0.7 (0.5-1.2)
Infant is father's first born (*n* = 587)	31.8% vs 33.5%	.68	0.9 (0.6-1.3)
Infant is a girl (*n* = 592)	**28.4% vs 36.3%**	**.04**	**0.7 (0.5-0.99)**

CI = confidence interval; OR = odds ratio.

depression was also associated with infant colic, and there was a borderline association between maternal anxiety and infant colic. Adjusting for maternal anxiety and depression did not attenuate the magnitude of association between maternal migraine and infant colic. Previous literature has demonstrated an association between maternal mood disorders and infant colic,[7,8,26,39] although directionality is difficult to disentangle, and some evidence suggests maternal depression may be a consequence of excessive infant crying.[8] Regardless, the observed association between maternal migraine and infant colic in this study does not appear to be due to confounding from these variables as it remained after controlling for them.

The finding of an association between maternal migraine and infant colic replicates the findings of our earlier study[2]—and does so in a larger sample that draws from a larger geographic area. Our previous study surveyed 154 mothers who were bringing their infants into 1 of 2 San Francisco based general pediatrics clinics for the 2-month well baby check. Mothers with migraine were more than twice as likely to have a baby with colic: 29% vs 11%, $P = .02$, with a prevalence ratio of 2.6 (95% CI 1.2-5.5).[2] The current study findings are also in line with those of a case-control study examining prenatal maternal risk factors for infant colic. In that study, 31/143 (21.7%) of mothers of babies with colic had a history of migraine vs 12/147 (8.2%) mothers of babies without colic, $P = .001$.[11]

In the current study, there was a "dose-response" in that mothers with migraine who had higher headache frequency were also more likely to have a baby with colic. For every 10-day increase in maternal headache frequency, odds of infant colic increased 60% (OR 1.6 (95% CI 1.1-2.4). The dose-effect is compelling evidence that there is a true association between maternal migraine and infant colic; however, as with all observational research the association may not be causal and the directionality of the relationship is not clear. It is possible that having a colicky baby could disrupt a mother's sleep and other self-care activities and thereby drive up migraine or headache frequency.

While maternal depression and anxiety were associated with infant colic in the maternal sample overall, within the subsample of the 300 mothers with migraine/probable migraine these variables were only numerically, but not statistically, associated with increased odds of infant colic in this study. To clarify the relationship between maternal mood disorders and infant colic within the population of mothers

with migraine, future research studies should aim to have a larger sample size of mothers with migraine.

Interestingly, having aura did not decrease the magnitude of the association between maternal migraine and infant colic. In the prospective Finnish cohort study, those individuals who had colic as infants were more likely to experience migraine without aura as adults but not more likely to experience migraine with aura.[20] Given that the migraine genes underlying migraine with aura vs migraine without aura are likely different,[40] we hypothesized that those migraine genes associated with infant colic would more likely be those of migraine without aura. It is possible that our negative finding was due to a relatively small sample size of mothers with aura (n = 124). However, in a retrospective case-control study that found that children with migraine were more likely to have had colic as infants, the association was seen both in those with migraine without aura (OR 7.0 (95% CI 4.4-11.1)) and those with migraine with aura (OR 5.7 (95% CI 3.1-10.7)).[19] Hence, there may be no true influence of aura on the relationship between migraine and colic.

Paternal migraine was not associated with infant colic in this study. In our previous, smaller study the observed data had suggested a possible association (prevalence ration (PR) 2.3 (95% CI 0.6-9.4)) but the sample size was small (n = 93) and the confidence intervals overlapped the null.[2] Our sample size in this study was considerably larger and this study was adequately powered to detect all but a small association, had it existed. Interestingly, fathers who reported having cried more as infants themselves were more likely to have migraine, but there was a substantial amount of missing data making this finding difficult to interpret.

In this study, fathers with anxiety or depression were more likely to have a baby with colic. The association between paternal depression and infant colic has been reported previously,[27] but the association between paternal anxiety and infant colic may be a novel observation as we have not seen this reported previously in the literature.

Notably, in this study fathers having a boy baby were more likely to report having a colicky baby. The majority of previous studies of infant colic have not found an effect of infant sex, and there was no effect of infant sex found in our maternal sample, thus it is possible this association was due to chance. It is also possible that fathers perceive infant crying behavior differently based on whether their baby is a boy or a girl, rather than the babies themselves crying differently. In a meta-analysis of 8 studies,[3] seven found no effect of infant sex while one found that boys were more likely to have colic (OR 1.6 (1.1-2.3)).[41] Additional research may be needed to clarify whether infant sex plays a role in some study populations.

Migraine is predominantly a genetic disorder in that there is usually a family history of the disease and there is a higher concordance rate among monozygotic twins compared to dizygotic twins.[24,42-44] Individuals with migraine are more sensitive to stimuli, both during and between attacks.[6,21,22] We have hypothesized previously that infants with colic may be those infants who have inherited a genetic predisposition toward migraine that has made their brains more sensitive to the stimuli they encounter outside the womb, and that they are expressing this sensitivity through excessive crying.[2,25] Seen as a neurodevelopmental process, crying might ramp up over the first weeks of life as the infant's perceptual abilities improve and they accordingly perceive more stimuli,[45] and then ultimately settle once they begin to consolidate sleep[46] and their brains can process and recover from over-stimulation more effectively.

However, if infant colic is indeed an early life manifestation of an inherited, amplified sensitivity to stimuli due to genes that ultimately manifest as migraine, it is not immediately obvious why an association between migraine and colic should be seen in mothers but not fathers. It is possible that the migraine genes involved in infant colic are mitochondrial[47-49] rather than autosomal, and therefore follow maternal inheritance patterns. Alternatively, the association may be due to an epigenetic phenomenon or one related to maternal hormone exposures in utero. It is also possible that mothers with migraine are more attuned to distressed infant crying than are fathers with migraine, and that it is really this amplified perceptual sensitivity in the mothers that accounts for the association rather than a true difference in the babies' amount of crying.

One of the limitations of this study is that we did not have an objective measure of infant crying time

(such as an audio-recording), but relied on parental report. However, parent-reported data on infant crying time is typically used in observational infant colic studies.[2,11,50,51] Even studies that use infant crying diaries share the limitation of being inherently subjective and reliant on parents' perception of infant crying. Hence it is difficult to untangle whether mothers with migraine are truly more likely to have babies who cry more, or whether phonophobia from migraine makes them more likely to perceive their babies as crying more. Future studies should use objective measures to record infant crying times.

Another potential limitation of our study is the lack of physician or healthcare professional diagnosis of migraine or any comorbidities. Instead we relied on the use of validated instruments when possible and participant self-report of having received a medical diagnosis of certain conditions. In addition, our assessment of the criteria for migraine and probable migraine are slightly modified from ICHD-3 criteria and our assessment of aura with migraine asks only about visual aura (which is the overwhelmingly most common type of aura experienced[31]), and did not include an upper time limit of 60 minutes as per ICHD-3 criteria. These are inherent limitations of web-based epidemiological studies which do not allow for in person assessment by a healthcare professional, medical chart review or prospective diaries, and is common practice for these types of studies.

Strengths of our study include the relatively large sample size and that our study population was drawn from almost every state in the United States, though a population-based study sample would have been optimal. We assessed comorbidities such as depression and anxiety that may confound the relationship between parental migraine and infant colic and utilized validated screening instruments to do so. Our methods for assessing migraine criteria are also well validated and adhered to modified International Classification of Headache Disorders, 3rd edition criteria. Our observed rates of migraine of 34.6% in mothers and 19.5% in fathers are in line with the cumulative lifetime incidence of migraine in the United States, which is estimated at 43% of women and 18% of men.[52] Similarly, in a pregnancy cohort study of 500 pregnant women, a lifetime history of migraine was seen in 20% and 29.8% had a history of migraine/probable migraine.[53]

The proportion of infants with colic in this study was higher than the 5-19% most commonly observed in other studies[2,3,50]—25.6% in the maternal sample and 32.6% in the paternal sample—though colic rates over 25% have been reported previously.[19,54] We used the same question for measuring colic in our first study and 14% of the infants in that study had colic,[2] so it does not seem to be an issue with the phrasing of the question. Parents with colicky babies may be more likely to participate in online studies that ask questions about infant crying. In an attempt not to over recruit parents with migraine or with colicky babies, our recruitment advertisements specifically did not mention headaches, migraine, crying or infant colic.

As with all observational studies, unmeasured or residual confounding is possible and our ability to draw causal inferences is limited. Further research will be needed to understand the mechanisms underlying our findings.

CONCLUSIONS

Maternal migraine is associated with infant colic; this has now been demonstrated in multiple studies. During pregnancy, mothers with migraine—particularly those with higher migraine frequency or a comorbid mood disorder—should be counseled about the possibility of having a colicky baby. Health care providers should also provide new parent(s) who have migraine with education and resources to help manage intense infant crying, including the knowledge that inconsolable infant crying is generally a time-limited phenomenon.

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