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A Population-Based Longitudinal Community Study of Major Depression and Migraine

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Conflict of interest statement

None of the authors have relevant conflicts of interest to report.

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Abbreviations

MDE - major depressive episodes, NPHS - National Population Health Survey, CIDI-SF - Composite International Diagnostic Interview Short Form, DSM-III-R - Diagnostic and Statistical Manual of Mental Disorders, 3th edition, revised, HR - hazard ratio, CI - confidence interval

Key words

migraine, depression, comorbidity, epidemiology, childhood trauma, stress

Abstract

Objective: To examine whether major depressive episodes (MDE) are associated with an increased risk of migraine in the general population and to examine whether migraine is associated with an increase risk of MDE.

Background: Population-based cross-sectional studies have consistently reported an association between migraine and depression. However, longitudinal studies about this potentially bidirectional association are inconsistent.

Methods: This retrospective cohort study used 12 years of follow-up data from the Canadian National Population Health Survey (15,254 respondents, age >12). Stratified analysis, logistic regression, and proportional hazard modeling were used to quantify the effect of migraine on subsequent MDE status and vice versa.

Results: After adjusting for sex, age, and other chronic health conditions, respondents with migraine were 60% more likely (HR 1.6, 95% CI 1.3-1.9) to develop MDE compared to those without migraine. Similarly adjusting for sex and age, respondents with MDE were 40% more likely (HR 1.4, 95% CI 1.0-1.9) to develop migraine compared to those without MDE. However, the latter association disappeared after adjustment for stress and childhood trauma.

Conclusions: The current study provides substantial evidence that migraine is associated with the later development of major depressive episodes, but does not provide strong causal evidence of an association in the other direction. Environmental factors such as childhood trauma and stress may shape the expression of this bidirectional relationship, however, the precise underlying mechanisms are not yet known.

Introduction

The association between major depressive episodes (MDE) and migraine has been observed in both population-based studies and in clinical settings[1-17]. Major depressive episodes in those with migraine may exacerbate the impact of the condition and complicate treatment[18] resulting in greater health resource use[14].

Population-based cross-sectional studies have consistently reported an association between migraine and MDE[1,10,11,13,14,19-22]. However, population-based longitudinal studies are often inconsistent in their methodological approaches and reporting of the association. First, although few in numbers, longitudinal studies consistently report an association between migraine and incident MDE. These studies generally show that migraine elevates the risk of MDE between four to six times[4,23]. Second, the literature about the longitudinal association between MDE and incident migraine is limited and the few studies on the topic show inconsistent findings. Patten[15] and Breslau[6,8] found that MDE increases the risk of incident migraine between two to six times. However, Swartz[12] found no association between MDE and incident migraine in the Baltimore Epidemiologic Catchment Area study, a study that may, however, have been underpowered to detect this association. The two studies from Michigan[6,8] found a significantly higher frequency of first onset migraine in respondents with MDE at baseline, as well as an effect in the other direction. These studies were based on samples from a health care organization and require replication in a general population sample. Furthermore, adjustment for additional covariates would help to confirm that this association is not due to confounding or shared causal effects of other variables. A study conducted using a birth cohort in Zurich[1,2] found an elevated risk of MDE in respondents with migraine, but did not estimate the incidence of migraine in people with MDE.

Several reasons make the current study a vital addition to the literature on this topic. First, the current study is based on a very large cohort. Thus, it is less likely to be underpowered, a potential issue with the Baltimore study, and also less likely to produce imprecise estimates. Second, unlike the Michigan studies[6,8], the current study is based on the general population. As such, it may have greater generalizability. Third, this study is inclusive of persons over the age of 12 at the 1994/1995 baseline interview rather than being limited to a cohort of individuals over the age of 17 at the start of the study[1,2,4,6,8,12]. This may be an important difference in view of the often young age of onset of both migraine and MDE. Finally, the length of follow-up, 12 years for the current study, is considerably longer than that of any of the prior longitudinal studies examining the association between MDE and migraine.

The objective of the current study was to examine whether major depressive episodes are associated with an increased risk of migraine in the general population and to examine whether migraine is associated with an increased risk of MDE.

Method

Data Source

The National Population Health Survey (NPHS) is a longitudinal study based on a nationally representative community sample assembled by Statistics Canada (Canada's national statistical agency) in 1994/1995. The NPHS interview is administered to a panel of individuals (cohort) who are followed over time to reflect the dynamic processes of health and illness[24]. Detailed information about the methods employed in this study may be found on the Statistics Canada Web page (http://www4.statcan.gc.ca/health-sante/fbs-rpe/fbs-rpe-eng.aspx). The NPHS cohort has been interviewed every 2 years and at the time of this analysis seven interviews were

available for the period 1994/1995-2006/2007. The longitudinal cohort included 17,276 participants, but the current analysis was restricted to *n*=15,254 respondents who were over the age of 12 years at the time of the initial 1994/1995 interview. This subset was further reduced to a 1) non-depressed cohort (*n*=13,175) in which respondents with MDE in 1994/1995 were excluded from the analysis in order to be able to assess incident MDE, and 2) a non-migraineur cohort (*n*=14,084) in which respondents with migraine in 1994/1995 were excluded from the analysis in order to be able to assess incident migraine. 1,262 participants were excluded because they did not provide information about either MDE (8.1%) or migraine (0.2%) status at baseline. Of those included, 13.3% died and 23.0% were lost to follow-up over the course of the 12 year study period.

Assessment of major depressive episodes

Major depressive episode was assessed by the number of depressive symptoms expressed by each respondent based on the DSM-III-R criteria as applied by the Composite International Diagnostic Interview Short Form (CIDI-SF). The NPHS interview included the CIDI-SF[25] to assess past year MDE. The CIDI-SF was administrated by experienced and trained Statistics Canada interviewers. The CIDI-SFMD was developed and validated at the University of Michigan[26,27]. The CIDI-SF is scored with a predictive probability based on the number of symptom-based criteria fulfilled during the same two week period in the past year. For the current analysis, if the estimated predicted probability was 0.9 or more, the respondent was considered to have experienced a MDE in the previous 12 months. The 90% predictive cut-point coincides with a respondent's reporting of five of the nine DSM-IV specified symptom-based criteria for MDE one of which needed to be depressed mood or loss of interest or pleasure. The

sensitivity and specificity of the CIDI-SF for major depression using this cut-point when compared against the full version of the CIDI has been found to be 90% and 94%, respectively[27].

Assessment of migraine

The NPHS interview included a series of items regarding long term medical conditions including migraine. The approach to assessment of chronic conditions is a standard one used by Statistics Canada, modelled after the approach used for the Centers for Disease Control Behavioral Risk Factor Surveillance System (http://www.cdc.gov/BRFSS/). Respondents were read the list of chronic medical conditions and asked where they had been diagnosed with one of these conditions by a health professional. The actual wording of the item was "Now, I would like to ask about certain chronic health conditions that you may have. We are interested in long-term conditions that have lasted, or are expected to last six months or more and that have been diagnosed by a health professional." This was followed by a series of specific questions including: "Remember, we're interested in conditions diagnosed by a health professional. Do you have migraine headaches?" Respondents answering *yes* to this question were identified as having migraine.

Other measures

A set of additional variables were include in the analysis because they were judged to be potential effect modifying or confounding variables. As a confounding variable must be an independent determinant of outcome and associated with exposure, variables thought to be associated with migraine or MDE were regarded as potential confounding variables depending on the analysis. Sex, age, marital status, household income, and educational attainment were included as covariates in the analysis. These variables were assessed using standard items,

extensively field-tested by Statistics Canada. Households with low income were identified using an income threshold, adjusted for household size. This represented, for example, a household income less than $15,000 for 1-2 person households and less than $30,000 for households with five or more members. Respondents were asked current and former smoking habits. The NPHS also included a smoking module leading to a dichotomous (never or former / current) smoking status variable.

The NPHS dataset also included a brief scale assessing self-esteem. This was a subset of 6 items from the Rosenberg's[28] original 10-item scale. The derived self-esteem scale had an internal consistency of α=0.85[29,30]. A four item social support scale was also included. This scale had an estimated internal consistency of α=0.64[31]. An 11 item chronic general stress scale included in the NPHS was a subset of items from a larger scale developed by Wheaton[32]. Items on the stress scale consisted of a series of statements about stressors (activity overload, financial difficulties, and problems with relationships). A score of one was assigned to each "true" response such that a higher score represented a greater level of stress. The scores were divided into quartiles; respondents classified in the upper quartile deemed to have a significant level of stress. A childhood trauma scale evaluated traumatic events during childhood or young adulthood: parental divorce, a lengthy hospital stay, prolonged parental unemployment, frequent parental alcohol or drug use. Chronic health conditions were identified using items similar to the migraine item, and responses to eighteen such conditions were included in this analysis. In cycle six (2004/2005) of the NPHS, respondents were asked if any of their close relatives (birth mother, birth father, birth brother, or birth sister) had been diagnosed with major depression by a health professional. We used the answers to these questions as an indicator for family history of MDE (any of the relatives had depression vs. no close relatives had depression).

Statistical Analysis

Two separate analyses were carried out to examine the bidirectional association between MDE and migraine. In the assessment of the outcome of incident MDE, migraine was treated as the exposure. Subjects who did not have MDE at the baseline interview were sorted into exposed and non-exposed cohorts based on migraine status at the baseline interview. The exposed (migraineur) and non-exposed (non-migraineur) cohorts were followed for 12 years in order to compare the incidence of MDE. In the assessment of incident migraine, subjects who did not report migraine at the baseline interview were sorted into exposed and non-exposed cohorts based on MDE status at baseline interview and then these depressed and non-depressed cohorts were followed for 12 years to compare the incidence of migraine.

Each condition under evaluation was assessed using the same methods. The methods of longitudinal analysis will therefore only be described here once (for incident MDE). The method of analysis was repeated in its entirety for the assessment of incident migraine. Estimates of relative risks (in the form of hazard ratios) of MDE in relation to migraine status, controlling for potential confounding variables, were obtained using proportional hazards modelling for grouped time data. The hazard ratio (HR) was modelled as a conditional probability that an individual with migraine experienced a target event (incident MDE) in any of the six discrete risk periods given that s/he did not experience the event at any earlier time period, divided by the same risk in those without migraine. In the NPHS, there were six interviews after the baseline interview, identifying six discrete (2 year) risk intervals. Proportional hazards modeling for grouped time data accounts for the assessment of MDE only at specific time points (every two years). Censored respondents would contribute varying lengths of study time depending on when they left the sampling frame, were lost to follow-up or developed MDE (at which point they are not

longer at risk and therefore leave the at risk cohort). The proportional hazards models were fit as generalized linear models of the binomial family with a complementary log-log function (Jenkins 1997). The proportional hazards assumption was evaluated using a likelihood ratio test for the significance of time-by-exposure (migraine) interactions. Migraine was treated as a time-varying factor so that migraine status at the start of each risk interval determined whether a respondent was in the exposed or in the non-exposed cohort during that interval. Since some people classified as not having migraine at baseline subsequently developed migraine, the time-varying definition is likely to involve less misclassification than the time-invariant definition. Selection of potential confounding variables was based initially on available epidemiologic evidence, but was constrained by the availability of measures of potential confounders in the NPHS. In general, variables that have been reported to be risk factors for MDE or migraine (depending on the analysis in question) were considered to be potential confounders. We initially conducted preliminary stratified analysis by comparing cumulative incidence across cohorts with stratification for these variables. Next, covariates were included in proportional hazards models one at a time. Confounding effects were considered to be present if stratification or model-based adjustment for a covariate resulted in a substantial change in the MDE-migraine association. Subsequently, models were created that included adjustment for more than one variable at a time. In the development of these more complex models, decisions about whether to include certain variables were determined by evidence of their possible confounding roles in the preceding stratified analysis and simpler models.

The NPHS used a multistage sampling procedure that resulted in unequal selection probability and potential correlations of measures within sampling units. To account for these design effects, data were weighted using replicate sampling weights provided by Statistics

Canada using a recommended bootstrap procedure[33]. The bootstrap procedure was used to calculate the variance of all estimates and in the assessment of statistical significance. In this study, 500 replicate bootstraps were used for each estimate, as recommended by Statistics Canada. All analysis and bootstrapping procedures were performed in STATA, version 11.0[34]. All analyses for this study were conducted at the Prairie RDC at the University of Calgary and were screened for approval prior to release. The study received approval from the University of Calgary Conjoint Ethics Board.

Results

The prevalence of MDE in the 1994 NPHS was 5.6%, comparable to the 4.8% annual prevalence reported from a Canadian national survey using a modification of the World Mental Health CIDI[35] interview. The age and sex distribution of MDE was also consistent with prior studies (female > male, declining annual prevalence with age). The overall prevalence of migraine in the 1994 sample resembled previous Canadian national estimates[14] with a weighted prevalence of 10.1% in women and 4.3% in men (compared to 15.2% and 6.1% previously reported[14]). Consistent with prior estimates, the peak prevalence of migraine was in the 25-44 age group (12.7% versus 13.1%[14]), followed by the 45-64 age group (11.1% versus 11.0%[14]).

We initially examined the cumulative incidence of MDE over the entire follow-up interval (among respondents without MDE at the baseline interview). Overall cumulative incidence was 15.2% (CI 14.0 – 16.2). This was substantially higher in those with migraine at baseline (22.2%, CI 18.0 – 26.5) than in those without (14.6%, CI 13.5 – 15.8). The cumulative incidence of migraine over the same interval was 12.4% (CI 11.5 – 13.5). Among those with

MDE at baseline the cumulative incidence of migraine was 24.7% (CI 19.2 – 30.0) compared to 11.9% (CI 10.8 – 12.9) in those without MDE.

Migraine as risk factor for MDE

In order to estimate the unadjusted HR for the effect of migraine on MDE risk, we initially fit a proportional hazards model that did not include any covariates. The proportional hazards assumption was evaluated using a likelihood ratio test for time-by-exposure interactions (migraine by each of the five indicator variables for the risk intervals). No violation of the proportional hazards assumption was identified. The unadjusted HR using the time-varying migraine definition was 2.1 (CI 1.7-2.5) indicating over the entire study period (1994/1995 to 2006/2007), people with migraine had 2.1 times the risk of developing MDE compared to those without migraine. The adjusted HR for incident MDE (1.8, CI 1.5-2.2) from the age and sex adjusted model was lower than both the unadjusted HR (2.1, CI 1.7-2.5) and the models adjusting for sex (1.9, CI 1.6-2.3) and age (2.0, CI 1.7-2.4) in isolation, see Table 1. Each of the variables considered to be potential confounders were significantly associated with incident MDE, with HRs ranging between 1.3 (chronic health conditions) to 2.2 (youngest age group, 12-25 compared to the 46+ age group). No significant interactions between any of these variables and migraine was found. Addition of these other variables: income, low self-esteem, low social support and childhood trauma resulted in no substantial change to the association except for addition of chronic conditions and family history of depression, adjustment for each of which reduced the age and sex adjusted migraine-MDE association from an HR of 1.8 to 1.6. The

association between migraine and MDE risk persisted after simultaneous adjustment for age, sex, chronic health conditions, and family history of depression (HR 1.4, CI 1.2-1.8), see Table 2.

MDE as risk factor for migraine

The unadjusted HR using time-varying MDE was 1.8 (CI 1.3-2.4). Over the entire study period (1994/1995 to 2006/2007), people with a history of MDE were 80% more likely to develop migraine compared to those without a history of MDE. No interactions between the identified covariates and MDE were found. The HR diminished slightly after adjustment for both sex and age (in each case HR 1.4, CI 1.0-1.9) suggesting confounding by these variables. Of the other variables examined: sex, age, stress, low income and childhood stress were associated with incident migraine, whereas smoking, obesity and chronic health conditions were not. Addition of stress to the age and sex adjusted model led to an adjusted HR of 1.3 (CI 1.0 – 1.8), p = 0.065. Addition of childhood trauma to the sex and age adjusted model made the association between MDE and migraine disappear (HR = 1.0, CI 0.7 – 1.4). The individual Wald tests for sex, age, stress, and childhood trauma remained significant in the models. Simultaneous adjustment for these covariates eliminated the association (HR 0.9, CI 0.7-1.2) between MDE and migraine, see Table 3. Results from the multivariate proportional hazards models (summarized in Table 4) show that the association between MDE and migraine risk disappears with the inclusion of stress or childhood trauma.

Discussion

This analysis identified a bidirectional association between MDE and migraine. Migraine is associated with an increased incidence of MDE and this association does not appear to be due to confounding by sex, age, chronic health conditions, or family history of depression. The sex

and age adjusted estimate of the association between migraine and incident MDE in the present study (HR 1.8,CI 1.5-2.2) is in the same direction as earlier studies[4,6]. However, the magnitude of the association is weaker than previously reported. Two other retrospective cohort studies of young adults previously reported sex adjusted HRs for migraine and incident MDE at 14 month and 3.5 year follow-up periods. The HRs for migraine and incident major depression in these studies were 4.2 (CI 2.0-9.2)[4] and 3.4 (CI 2.4-4.8)[6] respectively. A third retrospective cohort study reported an odds ratio, adjusted for sex and comorbid psychiatric disorders, of 5.2 (CI 2.4-11.3)[8], higher than the earlier studies and the current study. Methodological differences may account for the variation in the estimates between these earlier studies and this study. Furthermore, the wide confidence intervals around the point estimates of the earlier studies indicate lack of precision due to small sample sizes. The estimates from the present study are more precise due the larger sample size. As such, whereas the point estimates from prior studies may differ considerably from those reported here, the estimates are not necessarily inconsistent with one another. Given these methodological differences, the present study does confirm the association between migraine and incident MDE seen in earlier studies.

Previous studies[7,8,21] reported a significant bidirectional relationship between MDE and migraine. In the current study, the bidirectional association between MDE and migraine is weaker than in prior studies. Nevertheless, persons with one condition are still at greater risk of developing the other condition and vice versa. Sex and age adjusted estimates from this study indicate that persons with migraine are 80% more likely to develop MDE than persons without migraine. Persons with MDE are 40% more likely to develop migraine compared to persons without MDE. An attractive explanation for such bidirectional effects is the possible existence of shared risk factors. Therefore, this bidirectional association observed in this population-based

cohort study adds support to the suggestions of common neurobiology[36] or shared-etiology hypothesis[8]. Research about hypothesized shared etiologies has often focused on serotonergic function and glutaminergic transmitter systems[37-39] of the brain[40]. A recent Dutch genetic isolate study[37] attempted to determine whether the association between MDE and migraine was the result of heritable linkage[41]. This study concluded the heritability of migraine (particularly migraine with aura) could be due in part to a heritable component[41] linked to major depression. The Dutch study provides additional evidence that the bidirectional relationship between MDE and migraine may be partly explained by shared underlying genetically determined disease mechanisms[37].

The association between incident migraine and MDE disappeared entirely with additional adjustments for stress and childhood trauma. The disappearance of the association after adjustment for stress may be due to the introduction of bias. A biased estimate could result from the statistical adjustment for a factor such as stress that is caused, in part, by the exposure (MDE) under study if this same factor, stress, is also associated with the outcome of migraine. A weakening of effect such as that observed in the current study may be due to the occurrence of a causal chain of events, or due to confounding. Confounding would imply that stress is associated with MDE and happens to be a risk factor for migraine. In this case, adjustment for the variable as a confounder would be justified. However, to the extent that MDE contributes to the experience of stress, adjustment would be inappropriate and would underestimate the impact of MDE. Another possibility is that exposure to stress leads both to an increased risk of MDE and migraine, in other words this variable may be a shared risk factor. More detailed data would be required to fully isolate the temporal association between these variables. Whatever the exact

relationships, this study indicates that the contribution of MDE to migraine risk is not independent of childhood traumas and adult stressors.

In this study, the inclusion of childhood trauma attenuated the strength of the association between MDE and incident migraine making it no longer significant. The disappearance of the association after the adjustment for childhood trauma may indicate this factor acts as a confounder. However, childhood trauma may be a shared determinant for both MDE and migraine. Major depressive episodes may be a marker of neurobiologic changes secondary to childhood trauma that may also contribute to the etiology of migraine. Previous population-based studies have not addressed this issue. A recent Washington Twin study[40] about the shared genetic or environmental vulnerabilities underling migraine and major depression found a probable role of shared environmental factors in the etiology of major depression and/or migraine. The author noted that previous research[42] suggested that childhood maltreatment predisposed individuals to both major depression and migraine, hence, environmental factors may shape the expression of the bidirectional relationship. However, it is not possible to sharply distinguish between MDE in adulthood and the occurrence of childhood and adult stressors, which are factors that may themselves be entwined with the etiology and pathophysiology of MDE.

There are some limitations to our study. First, our cohort had a small proportion of non-responders and individuals lost to follow up. In prospective cohort studies, the primary sources of selection bias are non-response or loss to follow up[43]. However, a prior study about the NPHS data found attrition was related to several variables, but not to major depression or migraine[24]. The measures of MDE and migraine in the current study were not as sophisticated as those used in prior studies. If the NPHS included more misclassification errors than the prior studies, the estimated effects may have been diluted. Non-differential misclassification bias may account for

the lower HRs reported here as compared to earlier studies. Research has shown a stronger association between MDE and migraine with aura compared to migraine without aura[6,8,21]. The NPHS was not able to distinguish between different migraine types therefore this issue was beyond the scope of this study. Another issue involving measurement arises from the retrospective assessment of childhood traumas. Perceptions of childhood events may be vulnerable to distortion during an episode of depression occurring later in life. This may have increased the apparent prevalence of childhood trauma among those with MDE, potentially introducing bias into some of the adjusted estimates. Specifically, the apparent confounding effect of childhood traumas on association of MDE with subsequent migraine may have been exaggerated.

Furthermore, although International Headache Society criteria were not used in our study, our findings are in keeping with prior published reports on the epidemiology of migraine, suggesting that although migraine may have been under diagnosed, our estimates of the prevalence of migraine, as well as age and gender distributions, are still consistent with previously published epidemiological data. The degree to which the self-reported diagnosis of migraine were inaccurate because of reporting error is unknown, however, the estimates of prevalent migraine at each cycle (7.5% to 9.6%) in the NPHS are comparable to other cross-sectional Canadian studies[14,44,45] using a self reported health professional diagnosis of migraine. Some respondents suffering from chronic headaches might have been tallied as migraine sufferers and up to 50%[46,47] of respondents with migraine may not have been diagnosed by a health professional. It is possible in both of the scenarios that the misclassification of migraine could depend on MDE. If depressed respondents were more likely to report migraine diagnoses than non-depressed respondents, for example because of a tendency to somatise, this would

inflate the hazards ratio. If this type of bias was present in this study the estimates (HRs) may overestimate the true association between migraine and MDE.

The NPHS used an abbreviated measure (CIDI-SF) for MDE as opposed to the detailed full version of the CIDI. It has been noted that unlike the full version of the CIDI, the CIDI-SF does not exclude depressive moods due to physical illness or bereavement and may rarely be vulnerable to false positives[48]. However, the diagnostic accuracy of MDE is unlikely to differ depending on migraine status; the expected result is nondifferential misclassification bias. An additional limitation is that the CIDI-SF module for MDE does not cover other mental disorders, such as anxiety and substance use disorders. Anxiety disorders in particular tend to have their onset early in childhood and may have important clinical and epidemiologic implications.

Confounding may also have systematically affected the final estimates if variables other than those available in the NPHS dataset were associated with both migraine and MDE. It is possible that the final estimates presented in this study may be residually confounded by the effect of other psychiatric conditions on incident migraine. However, it was not possible to examine this using the NPHS data. This limitation reflects the mandate of the NPHS as a general health survey, as it was not designed to evaluate specific hypotheses, the covariates available for analyses such as this one are not fully comprehensive.

A strength of the present study is that measurements of MDE and migraine were repeated at two year follow-up intervals and occurred over a longer period than previous studies on the topic. Second, the high participation rate and sampling procedures employed by Statistics Canada make the results representative of a large proportion of Canadians. Third, this study examined the reciprocal relationship between MDE and migraine using the same cohort of people in a longitudinal study.

Multiple epidemiological studies including the current study have reported similar results suggesting a causal relationship between migraine and MDE risk. In view of this association between migraine and MDE, the next step should focus on exploring how this information can be used by clinicians. In particular, there should be feasibility and effectiveness studies about: primary prevention of MDE in the migraine population by improving migraine management; early detection of MDE in migraine clinic settings by heightening awareness of the association between MDE and migraine, or through formal case-finding efforts; consideration of treating migraineurs with MDE with a single agent that addresses both conditions to minimize side effects; and finally by ensuring access to mental health resources in settings where migraine is managed. Given the results from this study, it will be critical for future studies to include childhood trauma and stress as factors associated with MDE and migraine risk, especially to replicate and confirm the results reported. Evidence from biologically based studies is needed to clarify the mechanisms behind the association between MDE, migraine, stress, and childhood trauma. Future studies should also consider inclusion of biological measures such as brain imaging and stress hormone levels. Future studies should also address the major limitations of the current one. In future studies the diagnosis of migraine should be made using contemporary criteria, and should be based ideally on clinical assessment rather than self-report. Similarly, a full psychiatric diagnostic interview rather than a brief instrument should be employed. The scope of psychiatric assessment should also ideally be extended beyond MDE to examine a broader range of psychopathology. A particular concern is that childhood trauma is difficult to assess retrospectively, and that the associated pattern of psychiatric morbidity may include other conditions (such as anxiety disorders) having their onset during childhood. Longitudinal studies

starting in childhood and extending into the age range of peak incidence for depressive disorders and migraine may be a particularly promising strategy for future studies.

While the etiological connections between MDE and migraine risk needs further study, the results reported here confirm that the risk of migraine in those with MDE is elevated. Thus, clinicians and other health professionals should adopt strategies to address these multi-morbidities, such as case-finding, access to specialized care and using pharmacotherapy that treats both conditions to optimize benefits and potentially decrease side effect.

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Table 1 Comparison of unadjusted and adjusted HRs of migraine as risk factor for MDE

	HR	95% CI	p value
Unadjusted	*2.1*	*1.7-2.5*	<0.001
Adjusted, sex only	1.9	1.6-2.3	<0.001
Adjusted, sex & age	1.8	1.5-2.2	<0.001
Adjusted, sex, age & chronic health conditions	1.6	1.3-1.9	<0.001
Adjusted, sex, age & family history of depression	1.6	1.3-2.0	<0.001
Adjusted, sex, age, chronic health conditions, and family history of depression	1.4	1.2-1.8	<0.001

Table 2 Proportional hazards model describing migraine as a risk factor for MDE

	HR	95% CI	p value
Migraine (exposure)	*1.4*	*1.2-1.8*	<0.001
Female	1.6	1.3-1.9	<0.001
Age (0 = 46+, 1 = 12-25)	2.1	1.7-2.6	<0.001
Age (0 = 46+, 1 = 26-45)	1.6	1.3-2.0	<0.001
Chronic health conditions	1.3	1.1-1.5	<0.005
Family history of depression	1.8	1.5-2.2	<0.001

Table 3 Proportional hazards model describing MDE as a risk factor for migraine

	HR	95% CI	p value
MDE (exposure)	*0.9*	*0.7 - 1.2*	0.595
Female sex	2.6	2.2 - 3.2	<0.001
Age (0 = 46+, 1 = 12-25)	2.2	1.7 - 2.9	<0.001
Age (0 = 46+, 1 = 26-45)	1.9	1.6 - 2.3	<0.001
Stress	1.6	1.2 - 1.9	<0.001
Childhood trauma	1.2	1.0 - 1.5**	<0.05

Table 4 Comparison of unadjusted and adjusted HRs of MDE as risk factor for migraine

	HR	95% CI	p value
Unadjusted	*1.8*	*1.3 - 2.4*	<0.001
Adjusted, sex only	1.6	1.2 - 2.1	<0.005
Adjusted, sex & age	1.4	1.0 - 1.9	<0.05
Adjusted, sex, age, & stress	1.3	1.0 - 1.8	0.065
Adjusted, sex, age, & childhood trauma	1.0	0.7 - 1.4	0.962
Adjusted, sex, age, stress, & childhood trauma	0.9	0.6 - 1.2	0.595