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Assessing the Contribution of Stress to the Comorbidity of Migraine and Major Depression

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Abstract

Objectives: To estimate the comorbidity of migraine and major depression, and to assess how much this association may be explained by various measures of stress, including prior and current forms of acute and chronic stressors.

Design: National Population Health Survey is a prospective cohort study representative of the Canadian population followed from 1994/95, with surveys completed every two years through 2008/09.

Setting: Canadian adult population ages 18-64

Participants: 9,054 participants ages 18-64 years

Outcome: Incident migraine and major depression

Results: Adjusting for sex and age, depression was predictive of incident migraine (HR: 1.62; 95% CI: 1.03-2.53) and migraine was predictive of incident depression (HR: 1.55; 95% CI: 1.15-2.08). However, adjusting for each stressor we operationalized (childhood trauma, recent marital problems, recent unemployment, recent household financial problems, work stress, chronic stress, and change in social support) decreased this association, with chronic stress being a particularly strong covariate. After further adjusting for all stressors, both effects were largely attenuated and no longer significant (depression-migraine HR: 1.30; 95% CI: 0.80-2.10; migraine-depression HR: 1.19; 95% CI: 0.86-1.66).

Conclusions: While there appears to be temporal bidirectionality in the migraine-depression comorbidity, much of the apparent association is explained by stress.

ARTICLE SUMMARY

Article Focus

- To understand how much and what kinds of stressors play a role in explaining the comorbidity seen between migraine and major depression

Key Messages

- Migraine headache and major depression each predict the other prospectively
- Stress, particularly chronic stress, appears to explain much of the association seen between migraine and major depression

Strengths and Limitations

- Large, representative, prospective cohort study
- Migraine was self-reported with only a single question

INTRODUCTION

Several studies support that migraine and psychopathologies, in particular major depression, often co-occur.[1-15] A recent meta-analysis suggests the odds ratio may be near 2.2 for major depression and migraine.[16] While a correlation has been well established, the mechanisms for this occurrence are less clear. Given the breadth of studies finding this correlation, the comorbidity is likely explained by one or more of three paths: (1) a causal path from migraine to depression; (2) a causal path from depression to migraine; and/or (3) some shared common factor(s) cause both depression and migraine.

To begin assessing whether the presence of one disorder may lead to the development of the other, order of onset must be established, as temporality is necessary to establish causality. Prospective studies that examine both directions simultaneously are limited. Breslau and colleagues[7, 13] looked at the association between multiple headache types, including migraine, and major depression in a representative sample of middle-age adults. The authors found the association to be bidirectional, with migraine status predicting subsequent depression onset and vice versa. However, follow-up was only over a two-year period with just two assessments (baseline and two years later), limiting the understanding of this potential bidirectional association. Modgill and colleagues[15] have previously looked at migraine and major depression with twelve years of follow-up; they also found bidirectionality in their analyses. Other studies that have focused on specific patient samples and/or only a single direction of incidence find that anxiety onset precedes migraine onset, which may in turn precede major depression onset.[17-19]

However, the timeline between migraine and major depression is less clear in these studies, particularly because only one direction of onset was examined.

Meanwhile, shared risk factors are likely to explain some of the association between migraine and major depression.[20] Much attention has focused on a potentially shared genetic component,[21] although the comorbidity does not appear entirely explained by a genetic effect. Other research on shared common factors has focused on more structural or functional neurobiological differences that likely contribute to both disorders. One environmental factor that deserves further exploration is stress, which has known associations to major depression[22, 23] and migraine[15] in both chronic and acute forms. In the analyses presented by Modgill and colleagues,[15] some of the comorbidity appeared explained by childhood trauma and other stress, particularly for depression predicting migraine onset. However, their analyses only looked at a limited number of stressors and did not attempt to address specifically how much different types of stressors may contribute to this association.

The purposes of the current study are as follows: (1) to estimate the comorbidity of migraine and major depression in the adult Canadian population over an eight-year prospective follow-up period; and (2) to assess how much this association may be explained by various measures of stress, including prior and current forms of acute and chronic stressors.

METHODS

Sample

The National Population Health Survey (NPHS) is a prospective, nationally-representative study conducted by Statistics Canada that has followed a Canadian cohort since 1994/95. At study inception, individuals were randomly selected using a stratified two-stage sample design (n=17,276). The sample has been contacted every two years, with the most recent data collection in 2008/09. The response rate in the initial cycle of interview (1994/95) was 83.6%, with 63.6% of the original cohort still participating in 2006/07.[24, 25] Our research sample is restricted to the 9,054 individuals aged 18 to 64 years in Cycle 4 (2000/01; see Statistical Analyses for further explanation).

Depression

Major depressive episodes are assessed using the Composite International Diagnostic Interview Short Form for Major Depression (CIDI-SFMD) at all eight cycles. The CIDI-SFMD inquires about symptoms of major depression, as defined by the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), during the preceding 12 months. Kessler and colleagues[26] showed that the CIDI-SF has 93% classification accuracy for major depressive episode when compared with the full-length CIDI. Individuals who endorse five or more symptoms during a single two-week period are considered to have a 90% probability of having major depression;[26] for the purposes of this study, such individuals will be considered as having major depression in that year.

Migraine

Migraine is assessed in a single diagnostic question at each assessment. In the first three assessments (1994/95; 1996/97; 1998/99), subjects were asked whether they currently were having migraine headaches that had been diagnosed by a health professional. In the subsequent five assessments (2000/01; 2002/03; 2004/05; 2006/07; 2008/09), subjects were asked whether they currently have migraine headaches. In these last five assessments, subjects were further asked about the timing of onset of the diagnosis.

Stressors

Using similar definitions as previous studies using NPHS data,[23] we defined several types of stressors: childhood trauma, recent marital problems, recent unemployment, recent household financial problems, work stress, chronic stress, and change in social support. Childhood trauma was assessed in Cycle 1 (1994/95) for those 18 or older at that time, and in Cycle 4 (2000/01) for the rest of our cohort. Subjects were asked about seven items of childhood trauma occurring prior to the individual turning 18: parental divorce, a lengthy hospital stay, prolonged parental unemployment, frequent parental alcohol or drug use and physical abuse. Childhood trauma was categorized as none, one event, and two or more events. Three recent stressful life changes were defined: marital problems, recent unemployment, and household financial problems. Marital problems were defined by a change from reporting single, married, or partnered in Cycle 3 (1998/99) to divorced, widowed, or separated in Cycle 4 (2000/01). Recent unemployment was defined as being employed in Cycle 3 (1998/99) but reporting unemployment or not being in the labor force in Cycle 4 (2000/01). Household financial

problems were defined as having a score above Statistic Canada's low income cut-off (LICO) in Cycle 3 (1998/99) followed by a score below the cut-off in Cycle 4 (2000/01). The LICO score takes into account the individual's income relative to the community in which an individual lives and the size of their household.[24, 27] Work stress was measured in Cycle 4 (2000/01) by 13 questions that assessed job security, autonomy, conflict and satisfaction;[24] the score was categorized by quartiles. Chronic stress was measured in Cycle 4 (2000/01) by 18 questions that assessed stress in one's personal life, focusing primarily on relationships and family strife;[24] this score was also broken into quartiles. Social support was measured by a 4-question scale in Cycle 4 (2000/01);[24] this score was dichotomized at the median.

Statistical Analyses

For the purposes of this study, Cycle 4 (2000/01) is considered "baseline" in the presented analyses. This serves two purposes: (1) as both migraine and depression assessments reflect current states rather than diagnostic histories, this allows us to use the first three assessments to construct a several-year history of each disorder prior to baseline; and (2) as many of the stressors were not assessed until this time, this allows a more complete analysis of the role of stressors in the migraine-depression comorbidity.

We examined the onset of incident cases of a second condition relative to an index condition (among those with no history of the second condition). Cox Proportional Hazards Models were fit, and hazards ratios (HR) and their 95% confidence intervals (CI) are presented. Models are presented as unadjusted; adjusting for sex and age; adjusting for sex, age, and each stress exposure individually; and adjusting for sex, age, and all stress exposures. Data analyses were completed using SAS 9.2 and SUDAAN 10.0.1. All

estimates were weighted to adjust for unequal selection probabilities and cluster sampling; weights further adjust for attrition between the first and fourth cycle. Standard errors were calculated using the bootstrap method.

RESULTS

Demographic information is presented in **Table 1**. At baseline, 4.13, 9.13, and 1.33% of the sample reported current depression only, migraine only, and comorbid depression and migraine, respectively.

Models for depression status predicting incident migraine are presented in **Table 2**. Among non-migraineurs in Cycle 4 (2000/01), 5.52% developed migraine during the eight-year follow-up. The sex- and age-adjusted model suggested depression was predictive of incident migraine (HR: 1.62; 95% CI: 1.03-2.53). When adjusting further for stressors in separate models, estimates were further attenuated; adjusting for chronic stress attenuated the estimate the most (HR: 1.34; 95% CI: 0.84-2.13). When adjusting for all forms of stressors simultaneously, the depression-migraine estimate was attenuated by 19.75% (HR: 1.30; 95% CI: 0.80-2.10).

Models for migraine status predicting incident depression are presented in **Table 3**. Among subjects who had not had a depression up through Cycle 4 (2000/01), 8.72% developed incident depression. Migraine status was predictive of incident depression in the age- and sex-adjusted model (HR: 1.55; 95% CI: 1.15-2.08). Adjusting for stressors in separate models attenuated this relationship, with adjustment for chronic stress affecting the estimate the most (HR: 1.33; 95% CI: 0.98-1.79). The fully adjusted model estimate was attenuated by 23.23%, estimating a migraine-depression HR of 1.19 (95% CI: 0.86-1.66).

DISCUSSION

These results suggest there is an association between major depression and migraine. Without considering common causes or other explanations, these results align with earlier findings supporting a bidirectionality to this association: in crude analyses, migraine status predicted incident depression, and depression status predicted incident migraine. However, both directions of this relationship are largely explained by stressors that likely increase risk for both migraine and depression: adjusting for all measured forms of stress in these surveys attenuated the each estimate by about 20% and the associations were no longer significant after adjustment. Implications for research as well as clinical and public health practice are discussed.

Importantly, all stressors studied here did attenuate the results, suggesting that any form of stress may be an important common cause to consider when studying migraine and depression. This finding follows from prior research that supports both acute and chronic forms of stress as being confounders, since these have been shown to predict depression and migraine.[15, 22, 23] The present study suggests that ignoring these stressors collectively would have overestimated the migraine-depression association adjusted for known risk factors, and possibly concluded results were significant when they were not. Thus, research that does not account for these common causes when studying depression and migraine may be presenting misleading estimates.

While all types of stressors did attenuate the results, the strongest risk factor in both sets of models was chronic stress. This fits into a broader context of research suggesting that chronic stress may be causative of various types of chronic pain and major depression. In disentangling the relationship between depression, chronic stress,

and chronic pain such as fibromyalgia, its been proposed that chronic stress may lead to dysfunction in the hypothalamic-pituitary-adrenal axis, which in turn could lead to both depression and some forms of chronic pain.[28] Research specific to stress and migraine supports this biological theory.[29] Notably, childhood trauma was a strong risk factor in migraine predicting depression; as many of the types of trauma assessed were chronic in nature, this aligns with the finding that perhaps chronic forms of stress are especially potent common causes of migraine and depression.

Although certainly some of the crude association between depression and migraine may still be explained by genetics, other common causes, and/or biological pathways between the two disorders, the current findings suggest interesting considerations when developing future intervention strategies. Given the possibility of a biological mechanism between these two disorders, much research attention has been focused on the efficacy of antidepressant medications on preventing and managing migraine, with mixed success.[20, 30, 31] However, the current study suggests that perhaps a primary strategy could target reducing stress, particularly chronic stress, as this may both reduce the burden of the index disorder as well as potentially prevent the second condition from occurring. Indeed, there have been studies showing that various behavioural or stress management therapies (e.g., Cognitive-Behavioral Therapy) are effective treatments for migraine, supporting one aspect of this hypothesis.[32-34] Given how much chronic stress and other stressors seem to explain the comorbidity, such a strategy may have the potential for reducing this comorbidity burden on a larger scale than some of these other postulated pharmacological strategies, although further research actually comparing such treatment strategies would be needed.

The study has numerous strengths. This is one of only a few studies to prospectively assess the migraine-depression comorbidity bidirectionally,[7, 13, 15] and extends these previous findings by examining whether a rich assortment of well-validated stress measures explained the associations found. The nationally-representative nature of the study aids the generalizability of these findings, and the sample size and length of follow-up are exceptional. However, certain limitations warrant consideration. Migraine was assessed as only a single, self-reported question at each cycle. Ideally, a full battery of symptom-level diagnostic questions would have been available along with doctor diagnosis; however, the prevalence of migraine found in the NPHS is similar to that found in other Canadian studies.[14, 22] Nonetheless, self-report may be further inflated in depressed individuals, which may contribute to some overestimation in our associations. While the measure of major depression (CIDI-SFMD) has demonstrated psychometric properties,[26, 35] the 12-month diagnosis hinders inference about history of major depression, possible episodes unmeasured in the gap years of the study, and actual age of onset of the disorder. By using an interim cycle as "baseline", we were able to construct over a half decade profile of subjects' "history" of major depression to diminish the first issue. Finally, these analyses represent a rich assortment of stressors, but due to study design we were not able to fully address the time-varying nature of the relationships between stress and these episodic conditions. Given that we found acute, chronic, and prior (i.e., childhood trauma) stress to be relevant in this comorbidity, future research may wish to more closely examine the time-varying relationship between stress and these two conditions individually and comorbidly.

Understanding the causal mechanisms underlying the migraine-depression comorbidity may have a major public health impact. Major depression is a chief cause of disability worldwide,[36] estimated by the World Health Organization to become the second leading cause of disease burden by the year 2020.[37] Meanwhile, migraine affects 11% of the adult population, and when combined with other headache disorders also makes it into the top ten causes of disability by World Health Organization estimates.[38] Moreover, studies suggest that the disability and burden of these disorders may be compounded when present together.[11] Severity appears affected, as frequency and duration of migraine attacks have a significant association with psychiatric comorbidity.[39] Migraine patients with a mental health disorder report generally lower quality of life than other migraine patients;[2] in parallel, depression patients who report migraine also report poorer quality of life compared to other depression patients.[40] As such, implementation of effective stress-management strategies for migraineurs and those suffering from depression (as well as similar strategies to prevent the index disorder onset) may have major implications for prevention and intervention strategies that may lower the societal costs and burdens of both disorders.

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COMPETING INTERESTS

None declared

AUTHOR CONTRIBUTIONS

SS and IC conceived and designed the study and interpreted the results. SS and YZ performed the data analysis. SS wrote the manuscript. All authors critically reviewed the manuscript.

DATA SHARING STATEMENT

The data used for this study is housed and managed by Statistics Canada.

Table 1. Sample Characteristics Ages 18-64, % (SE)

Variable	% (SE)
N	9054
Sex	
Male	50.31 (0.17)
Female	49.69 (0.17)
Baseline Migraine/Depression Comorbidity	
None	85.41 (0.49)
Depression Only	4.13 (0.29)
Migraine Only	9.13 (0.40)
Depression and Migraine	1.33 (0.17)
Childhood Trauma	
0	49.61 (0.74)
1	25.82 (0.64)
2+	24.57 (0.65)
Recent Marital Change to Divorced, Separated, or Widowed	
Yes	2.47 (0.23)
No	97.53 (0.23)
Recent Unemployment	
Yes	4.34 (0.32)
No	95.66 (0.32)
Recent Change in Social Support	
Yes	16.76 (0.60)
No	83.24 (0.60)
Years of Follow-Up	
Median	7.30
IQR	6.29-7.67

Table 2. Adjusted hazard ratios for depression predicting migraine, adjusting for various stressors, age, and sex

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
Depression									
Yes	1.85 (1.20-2.85)	1.62 (1.03-2.53)	1.59 (1.03-2.46)	1.56 (0.98-2.47)	1.61 (1.02-2.53)	1.52 (0.97-2.38)	1.34 (0.84-2.13)	1.61 (1.02-2.54)	1.30 (0.80-2.10)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Childhood Trauma									
None			Reference						Reference
1			0.95 (0.66-1.37)						0.90 (0.60-1.33)
2+			1.34 (1.00-1.79)						1.09 (0.79-1.51)
Recent Marital Status Change									
Yes				1.54 (0.82-2.90)					1.28 (0.59-2.75)
No				Reference					Reference
Recent Unemployment									
Yes					1.00 (0.44-2.30)				0.72 (0.29-1.78)
No					Reference				Reference
Work Stress									
1st Quartile						Reference			Reference
2nd Quartile						0.63 (0.42-0.95)			0.61 (0.39-0.95)
3rd Quartile						0.66 (0.45-0.96)			0.63 (0.41-0.96)
4th Quartile						0.89 (0.61-1.31)			0.81 (0.52-1.27)
Chronic Stress									
1st Quartile							Reference		Reference
2nd Quartile							0.91 (0.59-1.40)		0.99 (0.63-1.56)
3rd Quartile							1.58 (1.11-2.25)		1.64 (1.12-2.41)
4th Quartile							1.76 (1.22-2.53)		1.68 (1.08-2.61)
Change in Social Support									
Yes								0.77 (0.54-1.11)	0.84 (0.58-1.21)
No								Reference	Refererence
Sex									
Male		Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female		2.39 (1.83-3.12)	2.34 (1.79-3.08)	2.49 (1.90-3.26)	2.44 (1.86-3.20)	2.28 (1.73-2.99)	2.39 (1.83-3.12)	2.48 (1.89-3.25)	2.32 (1.73-3.11)
Age (continuous)		0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)

Table 3. Adjusted hazard ratios for migraine predicting depression, adjusting for various stressors, age, and sex

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
Migraine									
Yes	1.84 (1.38-2.45)	1.55 (1.15-2.08)	1.43 (1.06-1.92)	1.46 (1.08-1.98)	1.54 (1.14-2.08)	1.51 (1.11-2.05)	1.33 (0.98-1.79)	1.46 (1.07-1.99)	1.19 (0.86-1.66)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Childhood Trauma									
None			Reference						Reference
1			1.23 (0.92-1.64)						1.14 (0.84-1.55)
2+			2.36 (1.79-3.12)						1.89 (1.38-2.59)
Recent Marital Status Change									
Yes				0.91 (0.40-2.06)					0.78 (0.33-1.84)
No				Reference					Reference
Recent Unemployed									
Yes					1.52 (0.93-2.49)				1.16 (0.68-1.99)
No					Reference				Reference
Work Stress									
1st Quartile						Reference			Reference
2nd Quartile						0.64 (0.48-0.85)			0.70 (0.52-0.95)
3rd Quartile						0.69 (0.50-0.94)			0.76 (0.55-1.06)
4th Quartile						1.12 (0.84-1.51)			1.06 (0.77-1.48)
Chronic Stress									
1st Quartile							Reference		Reference
2nd Quartile							1.45 (1.06-2.00)		1.47 (1.03-2.08)
3rd Quartile							2.02 (1.50-2.73)		1.89 (1.37-2.62)
4th Quartile							2.93 (2.20-3.88)		2.49 (1.80-3.44)
Change in Social Support									
Yes								0.91 (0.69-1.20)	0.94 (0.71-1.23)
No								Reference	Reference
Sex									
Male		Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female		1.91 (1.52-2.39)	1.86 (1.49-2.34)	1.94 (1.55-2.44)	1.92 (1.53-2.41)	1.80 (1.43-2.27)	1.89 (1.50-2.37)	1.89 (1.50-2.39)	1.83 (1.43-2.34)
Age (continuous)		0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

The Contribution of Stress to the Comorbidity of Migraine and Major Depression: Results from a Prospective Cohort Study

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The Contribution of Stress to the Comorbidity of Migraine and Major Depression: Results from a Prospective Cohort Study

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Keywords: migraine, major depression, stress, trauma

Abstract

Objectives: To estimate the comorbidity of migraine and major depression, and to assess how much this association may be explained by various measures of stress, including prior and current forms of stress.

Design: National Population Health Survey is a prospective cohort study representative of the Canadian population. Eight years of follow-up time were used in the present analyses.

Setting: Canadian adult population ages 18-64

Participants: 9,288 participants

Outcome: Incident migraine and major depression

Results: Adjusting for sex and age, depression was predictive of incident migraine (HR: 1.62; 95% CI: 1.03-2.53) and migraine was predictive of incident depression (HR: 1.55; 95% CI: 1.15-2.08). However, adjusting for each stressor we operationalized (childhood trauma, recent marital problems, recent unemployment, recent household financial problems, work stress, chronic stress, and change in social support) decreased this association, with chronic stress being a particularly strong covariate. After further adjusting for all stressors, both effects were largely attenuated and no longer significant (depression-migraine HR: 1.30; 95% CI: 0.80-2.10; migraine-depression HR: 1.19; 95% CI: 0.86-1.66).

Conclusions: While there appears to be temporal bidirectionality in the migraine-depression comorbidity, much of the apparent association is explained by stress.

ARTICLE SUMMARY

Article Focus

- To understand how much and what kinds of stressors play a role in explaining the comorbidity seen between migraine and major depression

Key Messages

- Migraine headache and major depression each predict the other prospectively
- Stress, particularly chronic stress, appears to explain much of the association seen between migraine and major depression

Strengths and Limitations

- Large, representative, prospective cohort study
- Migraine was self-reported with only a single question

INTRODUCTION

Several studies support that migraine and psychopathologies, in particular major depression, often co-occur.[1-15] In a recent review of such comorbidities, Antonaci et al reported a meta-analysis of 12 studies, concluding that the odds ratio may be near 2.2 for major depression and migraine.[16] A limited number of prospective studies have examined the temporality of this association, largely concluding the predictive relationship is bidirectional (i.e., migraine status predicts depression onset and vice versa).[1, 2, 10] While the correlation has been well established, the mechanisms for this co-occurrence are less clear; causal paths may exist from one disorder to the other, and/or some shared common risk factor(s) (i.e., confounders) may cause both depression and migraine.

Migraine and depression indeed share several risk factors, and thus any perceived correlation between the two could potentially be due to this confounding. Prior research assessing their association has adjusted primarily for demographic variables, however some studies have separately studied other risk factors of a genetic and neurobiologic nature. Few studies, however, have focused on stress, a known risk factor for both migraine and depression. In Modgill and colleagues' analyses of the National Population Health Survey (NPHS), a representative longitudinal study of the Canadian population, childhood trauma attenuated the association between the two disorders, particularly for the direction of depression predicting migraine onset.[10] However, their analyses only looked at a limited number of stressors and did not attempt to address specifically how much different types of stressors may contribute to this association. A variety of stressors may confound the migraine-depression association, as many types have been found to be

risk factors for both disorders: e.g., childhood trauma,[10, 17] unemployment,[18, 19] chronic/repeated stress,[20, 21] etc.

In the current study, we extend upon Modgill et al's findings in the NPHS to assess how much the association between migraine and depression may be explained by various measures of stress, including a wide variety of prior and current stressors. We assess this association longitudinally and bidirectionally.

METHODS

Sample

The NPHS is a prospective, nationally representative study conducted by Statistics Canada that has followed a Canadian cohort since 1994/95. At study inception, individuals were randomly selected using a stratified two-stage sample design (n=17,276). The sample has been contacted every two years, with the most recent data collection in 2008/09.

For the purposes of this study, we restricted our sample to individuals aged 18 to 64 years in Cycle 4 (2000/01), with this assessment treated as "baseline" in the presented analyses. This serves two purposes: (1) as both migraine and depression assessments reflect current states rather than diagnostic histories, this allows us to use the first three assessments to construct a several-year history of each disorder prior to baseline; and (2) as some of the stressors were not assessed until this time (e.g., work stress, chronic stress) or could not be constructed without at least two assessments (e.g., change in social support, marital status, or employment), this allows a more complete analysis of the role of stressors in the migraine-depression comorbidity. Further information on our analytic sample is depicted in **Figure 1**.

Depression

Major depressive episodes are assessed using the Composite International Diagnostic Interview Short Form for Major Depression (CIDI-SFMD) at all eight cycles. The CIDI-SFMD inquires about symptoms of major depression, as defined by the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), during the

preceding 12 months. Kessler and colleagues[22] showed that the CIDI-SF has 93% classification accuracy for major depressive episode when compared with the full-length CIDI. Individuals who endorse five or more symptoms during a single two-week period are considered to have a 90% probability of having major depression;[22] for the purposes of this study, such individuals will be considered as having major depression in that year.

Migraine

Migraine is assessed in a single diagnostic question at each assessment. In the first three assessments (1994/95; 1996/97; 1998/99), subjects were asked whether they currently were having migraine headaches that had been diagnosed by a health professional. In the subsequent five assessments (2000/01; 2002/03; 2004/05; 2006/07; 2008/09), subjects were asked whether they currently have migraine headaches. In these last five assessments, subjects were further asked about the timing of onset of the diagnosis.

Stressors

Using similar definitions as previous studies using NPHS data,[17] we defined several types of stressors: childhood trauma, recent marital problems, recent unemployment, recent household financial problems, work stress, chronic stress, and change in social support. Childhood trauma was assessed in Cycle 1 (1994/95) for those 18 or older at that time, and in Cycle 4 (2000/01) for the rest of our cohort. Subjects were asked about seven items of childhood trauma occurring prior to the individual turning 18: parental divorce, a lengthy hospital stay, prolonged parental unemployment, frequent parental alcohol or drug use and physical abuse. Childhood trauma was categorized as none, one event, and two or more events. Three recent stressful life changes were

defined: marital problems, recent unemployment, and household financial problems. Marital problems were defined by a change from reporting single, married, or partnered in Cycle 3 (1998/99) to divorced, widowed, or separated in Cycle 4 (2000/01). Recent unemployment was defined as being employed in Cycle 3 (1998/99) but reporting unemployment or not being in the labor force in Cycle 4 (2000/01). Household financial problems were defined as having a score above Statistic Canada's low income cut-off (LICO) in Cycle 3 (1998/99) followed by a score below the cut-off in Cycle 4 (2000/01). The LICO score takes into account the individual's income relative to the community in which an individual lives and the size of their household.[23, 24] Work stress was measured in Cycle 4 (2000/01) by 13 questions that assessed job security, autonomy, conflict and satisfaction;[24] the score was categorized by quartiles. Chronic stress was measured in Cycle 4 (2000/01) by 18 questions that assessed stress in one's personal life, focusing primarily on relationships and family strife;[24] this score was also broken into quartiles. Social support was measured by a 4-question scale in Cycles 3 and 4 (1998/99; 2000/01);[24] this score was dichotomized at the median, and change in social support was conceptualized as a change from high to low social support.

Statistical Analyses

We performed two sets of analyses. First, among those with no history of major depression (unweighted n=7,818), we assessed the onset of incident major depression comparing those with and without migraine at baseline; second, among those with no history of migraine (unweighted n=7,765), we assessed the onset of incident migraine comparing those with and without major depression at baseline. Cox Proportional Hazards Models were fit, and hazards ratios (HR) and their 95% confidence intervals (CI)

are presented. Models are presented as unadjusted; adjusting for sex and age; adjusting for sex, age, and each stress exposure individually; and adjusting for sex, age, and all stress exposures. Data analyses were completed using SAS 9.2 and SUDAAN 10.0.1. All estimates were weighted to adjust for unequal selection probabilities and cluster sampling; weights further adjust for attrition between the first and fourth cycle. Standard errors were calculated using the bootstrap method.

RESULTS

Demographic information is presented in **Table 1**. At baseline, 4.13, 9.13, and 1.33% of the sample reported current depression only, migraine only, and comorbid depression and migraine, respectively.

Models for depression status predicting incident migraine are presented in **Table 2**. Among non-migraineurs in Cycle 4 (2000/01), 5.52% developed migraine during the eight-year follow-up. The sex- and age-adjusted model suggested depression was predictive of incident migraine (HR: 1.62; 95% CI: 1.03-2.53). When adjusting further for stressors in separate models, estimates were further attenuated; adjusting for chronic stress attenuated the estimate the most (HR: 1.34; 95% CI: 0.84-2.13). When adjusting for all forms of stressors simultaneously, the depression-migraine estimate was attenuated by 19.75% (HR: 1.30; 95% CI: 0.80-2.10).

Models for migraine status predicting incident depression are presented in **Table 3**. Among subjects who had not had a depression up through Cycle 4 (2000/01), 8.72% developed incident depression. Migraine status was predictive of incident depression in the age- and sex-adjusted model (HR: 1.55; 95% CI: 1.15-2.08). Adjusting for stressors in separate models attenuated this relationship, with adjustment for chronic stress affecting the estimate the most (HR: 1.33; 95% CI: 0.98-1.79). The fully adjusted model estimate was attenuated by 23.23%, estimating a migraine-depression HR of 1.19 (95% CI: 0.86-1.66).

DISCUSSION

Without considering common causes or other explanations, these results align with earlier findings supporting a bidirectionality to a migraine-depression association: in crude analyses, migraine status predicted incident depression, and depression status predicted incident migraine. However, both directions of this relationship are largely explained by stressors that likely increase risk for both migraine and depression: adjusting for all measured forms of stress in these surveys attenuated the each estimate by about 20% and the associations were no longer significant after adjustment. Implications for research as well as clinical and public health practice are discussed.

Importantly, all stressors studied here did attenuate the results, suggesting that any form of stress may be an important common cause to consider when studying migraine and depression. This finding follows from prior research that supports both acute and chronic forms of stress as being confounders, since these have been shown to predict depression and migraine.[10, 17-21] The present study suggests that prior studies that these stressors collectively explain much of the perceived migraine-depression association; research that does not account for these common causes when studying depression and migraine may be presenting misleading estimates.

While all types of stressors did attenuate the results, the strongest risk factor in both sets of models was chronic stress. This fits into a broader context of research suggesting that chronic stress may be causative of various types of chronic pain and major depression. In disentangling the relationship between depression, chronic stress, and chronic pain such as fibromyalgia, its been proposed that chronic stress may lead to dysfunction in the hypothalamic-pituitary-adrenal axis, which in turn could lead to both

depression and some forms of chronic pain.[25] Research specific to stress and migraine supports this biological theory.[26] Notably, childhood trauma was a strong risk factor in migraine predicting depression; as many of the types of trauma assessed were chronic in nature, this aligns with the finding that perhaps chronic forms of stress are especially potent common causes of migraine and depression.

Although certainly some of the crude association between depression and migraine may still be explained by genetics, other common causes, and/or biological pathways between the two disorders, the current findings suggest interesting considerations when developing future intervention strategies. Given the possibility of a biological mechanism between these two disorders, much research attention has been focused on the efficacy of antidepressant medications on preventing and managing migraine, with mixed success.[27-29] However, the current study suggests that perhaps a primary strategy could target reducing stress, particularly chronic stress, as this may both reduce the burden of the index disorder as well as potentially prevent the second condition from occurring. Indeed, there have been studies showing that various behavioural or stress management therapies (e.g., Cognitive-Behavioral Therapy) are effective treatments for migraine, supporting one aspect of this hypothesis.[30-32] Given how much chronic stress and other stressors seem to explain the comorbidity, such a strategy may have the potential for reducing this comorbidity burden on a larger scale than some of these other postulated pharmacological strategies, although further research actually comparing such treatment strategies would be needed. Utilizing a stress-reducing strategy to address this comorbidity assumes that stress is (directly or indirectly)

causative of both disorders, while it is possible that stress is a risk factor through associations with a common cause.

The study has numerous strengths. This is one of only a few studies to prospectively assess the migraine-depression comorbidity bidirectionally,[1, 2, 10] and extends these previous findings by examining whether a rich assortment of widely-used stress measures explained the associations found. The nationally-representative nature of the study aids the generalizability of these findings, and the sample size and length of follow-up are exceptional.

However, certain limitations warrant consideration. Migraine was assessed as only a single, self-reported question at each cycle. Self-reported symptom-based assessments do generally report a higher prevalence than doctor diagnoses;[33] the assessment in the NPHS inquires about diagnosis by a health professional which may offset some of this over-reporting, but certainly misclassification may still be an issue. Specifically, self-report may be further inflated in depressed individuals, which may actually contribute to some overestimation in our associations. While the measure of major depression (CIDI-SFMD) has demonstrated psychometric properties,[22, 34, 35] the 12-month diagnosis (which thus does not cover the 2 years between each study assessment) hinders inference about history of major depression, possible episodes unmeasured in the gap years of the study, and actual timing of onset of the disorder; subjects who have less frequent depressive episodes or episodes that are shorter in duration would be less likely to be measured accurately. However, by using an interim cycle as "baseline", we were able to construct over a half-decade profile of subjects' "history" of major depression to diminish the issue regarding assessing history. Finally,

we did not have complete follow-up for all subjects. Weighting was used to correct for attrition between Cycles 1 and 4. From Cycle 4 through 8 the majority of subjects were assessed eight years later (see **Figure 1**), and follow-up duration was not associated with migraine or depression status at baseline. Follow-up duration, however, was associated with age and a few stressors (greater chronic stress, recent unemployment, and recent divorce were associated with shorter follow-up; p's<0.05); however, as stress likely predicts higher levels of the outcome disorders, its likely this implies that some subjects were censored prior to onset of the outcome, meaning that stress would explain even more of the association measured had complete follow-up occurred.

These analyses highlight considerations for future research. These analyses represent a rich assortment of stressors, but several other stressors may also merit examination, e.g., childhood sexual abuse, acute recent traumas such as injury or illness, etc. Further, as some of the stressors were only assessed in one or two cycles, we were not able to fully address the time-varying nature of the relationships between stress and these episodic conditions. Given that we found recent and prior stress to be relevant in this comorbidity, future research may wish to more closely examine the time-varying relationship between stress and these two conditions individually and comorbidly. Specifically, while stress is a risk factor for both disorders, it may also be caused by each disorder, and thus assessing temporal relationships using models that account for time-varying confounding appropriately (e.g., marginal structural models), may highlight the relationship between these variables further.

Understanding the causal mechanisms underlying the migraine-depression comorbidity may have a major public health impact. Major depression is a chief cause of

disability worldwide,[36] estimated by the World Health Organization to become the second leading cause of disease burden by the year 2020.[37] Meanwhile, migraine affects 11% of the adult population, and when combined with other headache disorders also makes it into the top ten causes of disability by World Health Organization estimates.[38] Moreover, studies suggest that the disability and burden of these disorders may be compounded when present together;[5] disease severity appears greater when these disorders are comorbid, e.g., frequency and duration of migraine attacks have a significant association with psychiatric comorbidity.[39] Migraine patients with a psychiatric disorder report generally lower quality of life than other migraine patients;[8] in parallel, depression patients who report migraine also report poorer quality of life compared to other depression patients.[40] As such, implementation of effective stress-management strategies for migraineurs and those suffering from depression (as well as similar strategies to prevent the index disorder onset) may have major implications for prevention and intervention strategies that may lower the societal costs and burdens of both disorders.

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COMPETING INTERESTS

None declared

AUTHOR CONTRIBUTIONS

SS and IC conceived and designed the study and interpreted the results. SS, YZ and MW performed the data analysis. SS wrote the manuscript. All authors critically reviewed the manuscript.

Table 1. Sample Characteristics Ages 18-64, % (SE)

Variable	Unweighted N	% (SE)
N	9,342	
Sex		
Male	4,986	50.31 (0.17)
Female	4,356	49.69 (0.17)
Age, mean (range)		40.77 (18-64)
Baseline Migraine/Depression Comorbidity		
None	7,619	85.41 (0.49)
Depression Only	404	4.13 (0.29)
Migraine Only	839	9.13 (0.40)
Depression and Migraine	124	1.33 (0.17)
Childhood Trauma		
0	4,194	49.61 (0.74)
1	2,265	25.82 (0.64)
2+	2,274	24.57 (0.65)
Recent Marital Change to Divorced, Separated, or Widowed		
Yes	214	2.47 (0.23)
No	8,781	97.53 (0.23)
Recent Unemployment		
Yes	394	4.34 (0.32)
No	8,670	95.66 (0.32)
Recent Change in Social Support		
Yes	1,359	16.76 (0.60)
No	6,961	83.24 (0.60)
Years of Follow-Up		
Median		7.30
IQR		6.29-7.67

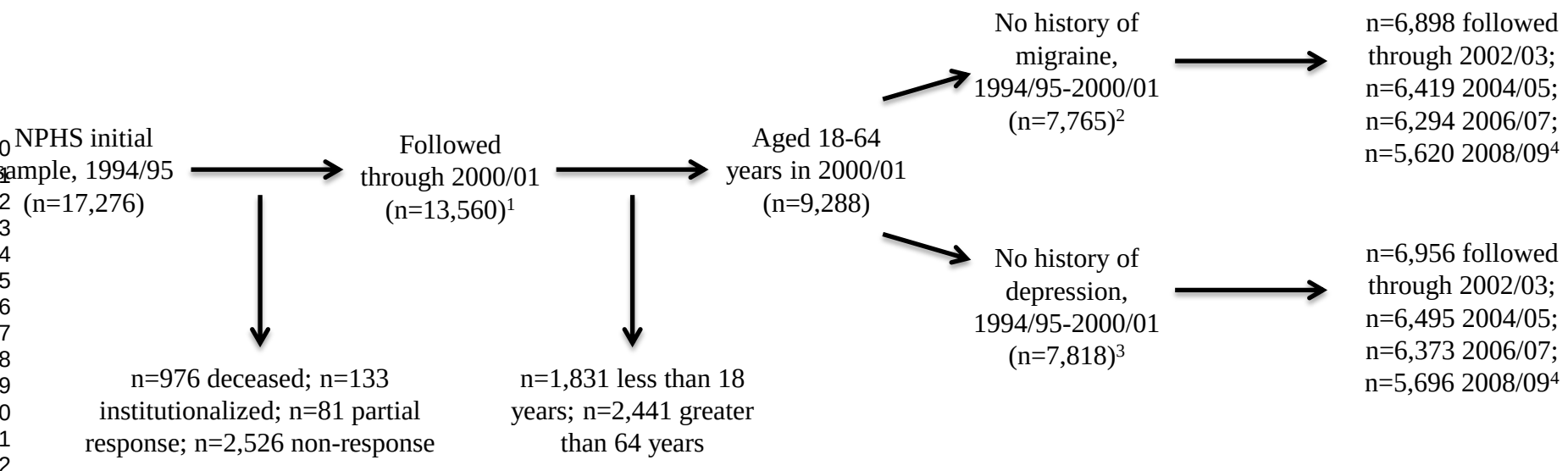
Table 2. Adjusted hazard ratios for depression predicting migraine, adjusting for various stressors, age, and sex

	Model 1 (n=7,076)	Model 2 (n=7,076)	Model 3 (n=6,678)	Model 4 (n=6,868)	Model 5 (n=6,953)	Model 6 (n=7,064)	Model 7 (n=7,044)	Model 8 (n=7,076)	Model 9 (n=6,339)
Depression									
Yes	1.85 (1.20-2.85)	1.62 (1.03-2.53)	1.59 (1.03-2.46)	1.56 (0.98-2.47)	1.61 (1.02-2.53)	1.52 (0.97-2.38)	1.34 (0.84-2.13)	1.61 (1.02-2.54)	1.30 (0.80-2.10)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Childhood Trauma									
None			Reference						Reference
1			0.95 (0.66-1.37)						0.90 (0.60-1.33)
2+			1.34 (1.00-1.79)						1.09 (0.79-1.51)
Recent Marital Status Change									
Yes				1.54 (0.82-2.90)					1.28 (0.59-2.75)
No				Reference					Reference
Recent Unemployment									
Yes					1.00 (0.44-2.30)				0.72 (0.29-1.78)
No					Reference				Reference
Work Stress									
1st Quartile						Reference			Reference
2nd Quartile						0.63 (0.42-0.95)			0.61 (0.39-0.95)
3rd Quartile						0.66 (0.45-0.96)			0.63 (0.41-0.96)
4th Quartile						0.89 (0.61-1.31)			0.81 (0.52-1.27)
Chronic Stress									
1st Quartile							Reference		Reference
2nd Quartile							0.91 (0.59-1.40)		0.99 (0.63-1.56)
3rd Quartile							1.58 (1.11-2.25)		1.64 (1.12-2.41)
4th Quartile							1.76 (1.22-2.53)		1.68 (1.08-2.61)
Change in Social Support									
Yes								0.77 (0.54-1.11)	0.84 (0.58-1.21)
No								Reference	Refererence
Sex									
Male		Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female		2.39 (1.83-3.12)	2.34 (1.79-3.08)	2.49 (1.90-3.26)	2.44 (1.86-3.20)	2.28 (1.73-2.99)	2.39 (1.83-3.12)	2.48 (1.89-3.25)	2.32 (1.73-3.11)
Age (continuous)		0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)

Table 3. Adjusted hazard ratios for migraine predicting depression, adjusting for various stressors, age, and sex

	Model 1 (n=7,339)	Model 2 (n=7,339)	Model 3 (n=6,840)	Model 4 (n=7,121)	Model 5 (n=7,176)	Model 6 (n=7,144)	Model 7 (n=7,127)	Model 8 (n=7,339)	Model 9 (n=6,387)
Migraine									
Yes	1.84 (1.38-2.45)	1.55 (1.15-2.08)	1.43 (1.06-1.92)	1.46 (1.08-1.98)	1.54 (1.14-2.08)	1.51 (1.11-2.05)	1.33 (0.98-1.79)	1.46 (1.07-1.99)	1.19 (0.86-1.66)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Childhood Trauma									
None			Reference						Reference
1			1.23 (0.92-1.64)						1.14 (0.84-1.55)
2+			2.36 (1.79-3.12)						1.89 (1.38-2.59)
Recent Marital Status Change									
Yes				0.91 (0.40-2.06)					0.78 (0.33-1.84)
No				Reference					Reference
Recent Unemployed									
Yes					1.52 (0.93-2.49)				1.16 (0.68-1.99)
No					Reference				Reference
Work Stress									
1st Quartile						Reference			Reference
2nd Quartile						0.64 (0.48-0.85)			0.70 (0.52-0.95)
3rd Quartile						0.69 (0.50-0.94)			0.76 (0.55-1.06)
4th Quartile						1.12 (0.84-1.51)			1.06 (0.77-1.48)
Chronic Stress									
1st Quartile							Reference		Reference
2nd Quartile							1.45 (1.06-2.00)		1.47 (1.03-2.08)
3rd Quartile							2.02 (1.50-2.73)		1.89 (1.37-2.62)
4th Quartile							2.93 (2.20-3.88)		2.49 (1.80-3.44)
Change in Social Support									
Yes								0.91 (0.69-1.20)	0.94 (0.71-1.23)
No								Reference	Reference
Sex									
Male		Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female		1.91 (1.52-2.39)	1.86 (1.49-2.34)	1.94 (1.55-2.44)	1.92 (1.53-2.41)	1.80 (1.43-2.27)	1.89 (1.50-2.37)	1.89 (1.50-2.39)	1.83 (1.43-2.34)
Age (continuous)		0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)

Figure 1. Flow diagram of sample inclusion and exclusion during study period



1. Analyses incorporate weights to account for attrition between 1994/95 and 2000/01 as well as unequal selection probabilities and cluster sampling from the initial study design.
2. Analyses of depression status in 2000/01 predicting migraine onset are performed on this sub-cohort.
3. Analyses of migraine status in 2000/01 predicting depression onset are performed on this sub-cohort.
4. Median follow-up time of participants aged 18-64 years in 2000/01 was 7.30 further years (IQR = 6.29-7.67).

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Check?	Recommendation
Title and abstract	x	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	x	Explain the scientific background and rationale for the investigation being reported
Objectives	x	State specific objectives, including any prespecified hypotheses
Methods		
Study design	x	Present key elements of study design early in the paper
Setting	x	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	x	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	x	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	x	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	x	Describe any efforts to address potential sources of bias
Study size	x	Explain how the study size was arrived at
Quantitative variables	x	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	x	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	x	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	x	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	x	Report numbers of outcome events or summary measures over

		time
Main results	x	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	x	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	x	Summarise key results with reference to study objectives
Limitations	x	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	x	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	x	Discuss the generalisability (external validity) of the study results
Other information		
Funding	x	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

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Tables: 3

Figures: 1

The Contribution of Stress to the Comorbidity of Migraine and Major Depression: Results from a Prospective Cohort Study

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Keywords: migraine, major depression, stress, trauma

Abstract

Objectives: To estimate the comorbidity of migraine and major depression, and to assess how much this association may be explained by various measures of stress, including prior and current forms of stress.

Design: National Population Health Survey is a prospective cohort study representative of the Canadian population. Eight years of follow-up time were used in the present analyses.

Setting: Canadian adult population ages 18-64

Participants: 9,288 participants

Outcome: Incident migraine and major depression

Results: Adjusting for sex and age, depression was predictive of incident migraine (HR: 1.62; 95% CI: 1.03-2.53) and migraine was predictive of incident depression (HR: 1.55; 95% CI: 1.15-2.08). However, adjusting for each stressor we operationalized (childhood trauma, recent marital problems, recent unemployment, recent household financial problems, work stress, chronic stress, and change in social support) decreased this association, with chronic stress being a particularly strong covariate. After further adjusting for all stressors, both effects were largely attenuated and no longer significant (depression-migraine HR: 1.30; 95% CI: 0.80-2.10; migraine-depression HR: 1.19; 95% CI: 0.86-1.66).

Conclusions: While there appears to be temporal bidirectionality in the migraine-depression comorbidity, much of the apparent association is explained by stress.

ARTICLE SUMMARY

Article Focus

- To understand how much and what kinds of stressors play a role in explaining the comorbidity seen between migraine and major depression

Key Messages

- Migraine headache and major depression each predict the other prospectively
- Stress, particularly chronic stress, appears to explain much of the association seen between migraine and major depression

Strengths and Limitations

- Large, representative, prospective cohort study
- Migraine was self-reported with only a single question

INTRODUCTION

Several studies support that migraine and psychopathologies, in particular major depression, often co-occur.[1-15] In a recent review of such comorbidities, Antonaci et al reported a meta-analysis of 12 studies, concluding that the odds ratio may be near 2.2 for major depression and migraine.[16] A limited number of prospective studies have examined the temporality of this association, largely concluding the predictive relationship is bidirectional (i.e., migraine status predicts depression onset and vice versa).[1, 2, 10] While the correlation has been well established, the mechanisms for this co-occurrence are less clear; causal paths may exist from one disorder to the other, and/or some shared common risk factor(s) (i.e., confounders) may cause both depression and migraine.

Migraine and depression indeed share several risk factors, and thus any perceived correlation between the two could potentially be due to this confounding. Prior research assessing their association has adjusted primarily for demographic variables, however some studies have separately studied other risk factors of a genetic and neurobiologic nature. Few studies, however, have focused on stress, a known risk factor for both migraine and depression. In Modgill and colleagues' analyses of the National Population Health Survey (NPHS), a representative longitudinal study of the Canadian population, childhood trauma attenuated the association between the two disorders, particularly for the direction of depression predicting migraine onset.[10] However, their analyses only looked at a limited number of stressors and did not attempt to address specifically how much different types of stressors may contribute to this association. A variety of stressors may confound the migraine-depression association, as many types have been found to be

risk factors for both disorders: e.g., childhood trauma,[10, 17] unemployment,[18, 19] chronic/repeated stress,[20, 21] etc.

In the current study, we extend upon Modgill et al's findings in the NPHS to assess how much the association between migraine and depression may be explained by various measures of stress, including a wide variety of prior and current stressors. We assess this association longitudinally and bidirectionally.

METHODS

Sample

The NPHS is a prospective, nationally representative study conducted by Statistics Canada that has followed a Canadian cohort since 1994/95. At study inception, individuals were randomly selected using a stratified two-stage sample design (n=17,276). The sample has been contacted every two years, with the most recent data collection in 2008/09.

For the purposes of this study, we restricted our sample to individuals aged 18 to 64 years in Cycle 4 (2000/01), with this assessment treated as "baseline" in the presented analyses. This serves two purposes: (1) as both migraine and depression assessments reflect current states rather than diagnostic histories, this allows us to use the first three assessments to construct a several-year history of each disorder prior to baseline; and (2) as some of the stressors were not assessed until this time (e.g., work stress, chronic stress) or could not be constructed without at least two assessments (e.g., change in social support, marital status, or employment), this allows a more complete analysis of the role of stressors in the migraine-depression comorbidity. Further information on our analytic sample is depicted in Figure 1.

Depression

Major depressive episodes are assessed using the Composite International Diagnostic Interview Short Form for Major Depression (CIDI-SFMD) at all eight cycles. The CIDI-SFMD inquires about symptoms of major depression, as defined by the

Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), during the preceding 12 months. Kessler and colleagues[22] showed that the CIDI-SF has 93% classification accuracy for major depressive episode when compared with the full-length CIDI. Individuals who endorse five or more symptoms during a single two-week period are considered to have a 90% probability of having major depression;[22] for the purposes of this study, such individuals will be considered as having major depression in that year.

Migraine

Migraine is assessed in a single diagnostic question at each assessment. In the first three assessments (1994/95; 1996/97; 1998/99), subjects were asked whether they currently were having migraine headaches that had been diagnosed by a health professional. In the subsequent five assessments (2000/01; 2002/03; 2004/05; 2006/07; 2008/09), subjects were asked whether they currently have migraine headaches. In these last five assessments, subjects were further asked about the timing of onset of the diagnosis.

Stressors

Using similar definitions as previous studies using NPHS data,[17] we defined several types of stressors: childhood trauma, recent marital problems, recent unemployment, recent household financial problems, work stress, chronic stress, and change in social support. Childhood trauma was assessed in Cycle 1 (1994/95) for those 18 or older at that time, and in Cycle 4 (2000/01) for the rest of our cohort. Subjects were asked about seven items of childhood trauma occurring prior to the individual turning 18: parental divorce, a lengthy hospital stay, prolonged parental unemployment, frequent parental alcohol or drug use and physical abuse. Childhood trauma was categorized as

none, one event, and two or more events. Three recent stressful life changes were defined: marital problems, recent unemployment, and household financial problems. Marital problems were defined by a change from reporting single, married, or partnered in Cycle 3 (1998/99) to divorced, widowed, or separated in Cycle 4 (2000/01). Recent unemployment was defined as being employed in Cycle 3 (1998/99) but reporting unemployment or not being in the labor force in Cycle 4 (2000/01). Household financial problems were defined as having a score above Statistic Canada's low income cut-off (LICO) in Cycle 3 (1998/99) followed by a score below the cut-off in Cycle 4 (2000/01). The LICO score takes into account the individual's income relative to the community in which an individual lives and the size of their household.[23, 24] Work stress was measured in Cycle 4 (2000/01) by 13 questions that assessed job security, autonomy, conflict and satisfaction;[24] the score was categorized by quartiles. Chronic stress was measured in Cycle 4 (2000/01) by 18 questions that assessed stress in one's personal life, focusing primarily on relationships and family strife;[24] this score was also broken into quartiles. Social support was measured by a 4-question scale in Cycles 3 and 4 (1998/99; 2000/01);[24] this score was dichotomized at the median, and change in social support was conceptualized as a change from high to low social support.

Statistical Analyses

We performed two sets of analyses. First, among those with no history of major depression (unweighted n=7,818), we assessed the onset of incident major depression comparing those with and without migraine at baseline; second, among those with no history of migraine (unweighted n=7,765), we assessed the onset of incident migraine comparing those with and without major depression at baseline. Cox Proportional

Hazards Models were fit, and hazards ratios (HR) and their 95% confidence intervals (CI) are presented. Models are presented as unadjusted; adjusting for sex and age; adjusting for sex, age, and each stress exposure individually; and adjusting for sex, age, and all stress exposures. Data analyses were completed using SAS 9.2 and SUDAAN 10.0.1. All estimates were weighted to adjust for unequal selection probabilities and cluster sampling; weights further adjust for attrition between the first and fourth cycle. Standard errors were calculated using the bootstrap method.

RESULTS

Demographic information is presented in **Table 1**. At baseline, 4.13, 9.13, and 1.33% of the sample reported current depression only, migraine only, and comorbid depression and migraine, respectively.

Models for depression status predicting incident migraine are presented in **Table 2**. Among non-migraineurs in Cycle 4 (2000/01), 5.52% developed migraine during the eight-year follow-up. The sex- and age-adjusted model suggested depression was predictive of incident migraine (HR: 1.62; 95% CI: 1.03-2.53). When adjusting further for stressors in separate models, estimates were further attenuated; adjusting for chronic stress attenuated the estimate the most (HR: 1.34; 95% CI: 0.84-2.13). When adjusting for all forms of stressors simultaneously, the depression-migraine estimate was attenuated by 19.75% (HR: 1.30; 95% CI: 0.80-2.10).

Models for migraine status predicting incident depression are presented in **Table 3**. Among subjects who had not had a depression up through Cycle 4 (2000/01), 8.72% developed incident depression. Migraine status was predictive of incident depression in the age- and sex-adjusted model (HR: 1.55; 95% CI: 1.15-2.08). Adjusting for stressors in separate models attenuated this relationship, with adjustment for chronic stress affecting the estimate the most (HR: 1.33; 95% CI: 0.98-1.79). The fully adjusted model estimate was attenuated by 23.23%, estimating a migraine-depression HR of 1.19 (95% CI: 0.86-1.66).

DISCUSSION

Without considering common causes or other explanations, these results align with earlier findings supporting a bidirectionality to a migraine-depression association: in crude analyses, migraine status predicted incident depression, and depression status predicted incident migraine. However, both directions of this relationship are largely explained by stressors that likely increase risk for both migraine and depression: adjusting for all measured forms of stress in these surveys attenuated the each estimate by about 20% and the associations were no longer significant after adjustment. Implications for research as well as clinical and public health practice are discussed.

Importantly, all stressors studied here did attenuate the results, suggesting that any form of stress may be an important common cause to consider when studying migraine and depression. This finding follows from prior research that supports both acute and chronic forms of stress as being confounders, since these have been shown to predict depression and migraine.[10, 17-21] The present study suggests that prior studies that these stressors collectively explain much of the perceived migraine-depression association; research that does not account for these common causes when studying depression and migraine may be presenting misleading estimates.

While all types of stressors did attenuate the results, the strongest risk factor in both sets of models was chronic stress. This fits into a broader context of research suggesting that chronic stress may be causative of various types of chronic pain and major depression. In disentangling the relationship between depression, chronic stress, and chronic pain such as fibromyalgia, its been proposed that chronic stress may lead to dysfunction in the hypothalamic-pituitary-adrenal axis, which in turn could lead to both

depression and some forms of chronic pain.[25] Research specific to stress and migraine supports this biological theory.[26] Notably, childhood trauma was a strong risk factor in migraine predicting depression; as many of the types of trauma assessed were chronic in nature, this aligns with the finding that perhaps chronic forms of stress are especially potent common causes of migraine and depression.

Although certainly some of the crude association between depression and migraine may still be explained by genetics, other common causes, and/or biological pathways between the two disorders, the current findings suggest interesting considerations when developing future intervention strategies. Given the possibility of a biological mechanism between these two disorders, much research attention has been focused on the efficacy of antidepressant medications on preventing and managing migraine, with mixed success.[27-29] However, the current study suggests that perhaps a primary strategy could target reducing stress, particularly chronic stress, as this may both reduce the burden of the index disorder as well as potentially prevent the second condition from occurring. Indeed, there have been studies showing that various behavioural or stress management therapies (e.g., Cognitive-Behavioral Therapy) are effective treatments for migraine, supporting one aspect of this hypothesis.[30-32] Given how much chronic stress and other stressors seem to explain the comorbidity, such a strategy may have the potential for reducing this comorbidity burden on a larger scale than some of these other postulated pharmacological strategies, although further research actually comparing such treatment strategies would be needed. Utilizing a stress-reducing strategy to address this comorbidity assumes that stress is (directly or indirectly)

causative of both disorders, while it is possible that stress is a risk factor through associations with a common cause.

The study has numerous strengths. This is one of only a few studies to prospectively assess the migraine-depression comorbidity bidirectionally,[1, 2, 10] and extends these previous findings by examining whether a rich assortment of widely-used stress measures explained the associations found. The nationally-representative nature of the study aids the generalizability of these findings, and the sample size and length of follow-up are exceptional.

However, certain limitations warrant consideration. Migraine was assessed as only a single, self-reported question at each cycle. Self-reported symptom-based assessments do generally report a higher prevalence than doctor diagnoses;[33] the assessment in the NPHS inquires about diagnosis by a health professional which may offset some of this over-reporting, but certainly misclassification may still be an issue. Specifically, self-report may be further inflated in depressed individuals, which may actually contribute to some overestimation in our associations. While the measure of major depression (CIDI-SFMD) has demonstrated psychometric properties,[22, 34, 35] the 12-month diagnosis (which thus does not cover the 2 years between each study assessment) hinders inference about history of major depression, possible episodes unmeasured in the gap years of the study, and actual timing of onset of the disorder; subjects who have less frequent depressive episodes or episodes that are shorter in duration would be less likely to be measured accurately. However, by using an interim cycle as "baseline", we were able to construct over a half-decade profile of subjects' "history" of major depression to diminish the issue regarding assessing history. Finally,

we did not have complete follow-up for all subjects. Weighting was used to correct for attrition between Cycles 1 and 4. From Cycle 4 through 8 the majority of subjects were assessed eight years later (see Figure 1), and follow-up duration was not associated with migraine or depression status at baseline. Follow-up duration, however, was associated with age and a few stressors (greater chronic stress, recent unemployment, and recent divorce were associated with shorter follow-up; *p*'s<0.05); however, as stress likely predicts higher levels of the outcome disorders, its likely this implies that some subjects were censored prior to onset of the outcome, meaning that stress would explain even more of the association measured had complete follow-up occurred.

These analyses highlight considerations for future research. These analyses represent a rich assortment of stressors, but several other stressors may also merit examination, e.g., childhood sexual abuse, acute recent traumas such as injury or illness, etc. Further, as some of the stressors were only assessed in one or two cycles, we were not able to fully address the time-varying nature of the relationships between stress and these episodic conditions. Given that we found recent and prior stress to be relevant in this comorbidity, future research may wish to more closely examine the time-varying relationship between stress and these two conditions individually and comorbidly. Specifically, while stress is a risk factor for both disorders, it may also be caused by each disorder, and thus assessing temporal relationships using models that account for time-varying confounding appropriately (e.g., marginal structural models), may highlight the relationship between these variables further.

Understanding the causal mechanisms underlying the migraine-depression comorbidity may have a major public health impact. Major depression is a chief cause of

disability worldwide,[36] estimated by the World Health Organization to become the second leading cause of disease burden by the year 2020.[37] Meanwhile, migraine affects 11% of the adult population, and when combined with other headache disorders also makes it into the top ten causes of disability by World Health Organization estimates.[38] Moreover, studies suggest that the disability and burden of these disorders may be compounded when present together;[5] disease severity appears greater when these disorders are comorbid, e.g., frequency and duration of migraine attacks have a significant association with psychiatric comorbidity.[39] Migraine patients with a psychiatric disorder report generally lower quality of life than other migraine patients;[8] in parallel, depression patients who report migraine also report poorer quality of life compared to other depression patients.[40] As such, implementation of effective stress-management strategies for migraineurs and those suffering from depression (as well as similar strategies to prevent the index disorder onset) may have major implications for prevention and intervention strategies that may lower the societal costs and burdens of both disorders.

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COMPETING INTERESTS

None declared

AUTHOR CONTRIBUTIONS

SS and IC conceived and designed the study and interpreted the results. SS, YZ and MW~~YZ~~ performed the data analysis. SS wrote the manuscript. All authors critically reviewed the manuscript.

Table 1. Sample Characteristics Ages 18-64, % (SE)

Variable	Unweighted N	% (SE)
N	9,342	
Sex		
Male	4,986	50.31 (0.17)
Female	4,356	49.69 (0.17)
Age, mean (range)		40.77 (18-64)
Baseline Migraine/Depression Comorbidity		
None	7,619	85.41 (0.49)
Depression Only	404	4.13 (0.29)
Migraine Only	839	9.13 (0.40)
Depression and Migraine	124	1.33 (0.17)
Childhood Trauma		
0	4,194	49.61 (0.74)
1	2,265	25.82 (0.64)
2+	2,274	24.57 (0.65)
Recent Marital Change to Divorced, Separated, or Widowed		
Yes	214	2.47 (0.23)
No	8,781	97.53 (0.23)
Recent Unemployment		
Yes	394	4.34 (0.32)
No	8,670	95.66 (0.32)
Recent Change in Social Support		
Yes	1,359	16.76 (0.60)
No	6,961	83.24 (0.60)
Years of Follow-Up		
Median		7.30
IQR		6.29-7.67

Table 2. Adjusted hazard ratios for depression predicting migraine, adjusting for various stressors, age, and sex

	Model 1 (n=7,076)	Model 2 (n=7,076)	Model 3 (n=6,678)	Model 4 (n=6,868)	Model 5 (n=6,953)	Model 6 (n=7,064)	Model 7 (n=7,044)	Model 8 (n=7,076)	Model 9 (n=6,339)
Depression									
Yes	1.85 (1.20-2.85)	1.62 (1.03-2.53)	1.59 (1.03-2.46)	1.56 (0.98-2.47)	1.61 (1.02-2.53)	1.52 (0.97-2.38)	1.34 (0.84-2.13)	1.61 (1.02-2.54)	1.30 (0.80-2.10)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Childhood Trauma									
None			Reference						Reference
1			0.95 (0.66-1.37)						0.90 (0.60-1.33)
2+			1.34 (1.00-1.79)						1.09 (0.79-1.51)
Recent Marital Status Change									
Yes				1.54 (0.82-2.90)					1.28 (0.59-2.75)
No				Reference					Reference
Recent Unemployment									
Yes					1.00 (0.44-2.30)				0.72 (0.29-1.78)
No					Reference				Reference
Work Stress									
1st Quartile						Reference			Reference
2nd Quartile						0.63 (0.42-0.95)			0.61 (0.39-0.95)
3rd Quartile						0.66 (0.45-0.96)			0.63 (0.41-0.96)
4th Quartile						0.89 (0.61-1.31)			0.81 (0.52-1.27)
Chronic Stress									
1st Quartile							Reference		Reference
2nd Quartile							0.91 (0.59-1.40)		0.99 (0.63-1.56)
3rd Quartile							1.58 (1.11-2.25)		1.64 (1.12-2.41)
4th Quartile							1.76 (1.22-2.53)		1.68 (1.08-2.61)
Change in Social Support									
Yes								0.77 (0.54-1.11)	0.84 (0.58-1.21)
No								Reference	Refererence
Sex									
Male		Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female		2.39 (1.83-3.12)	2.34 (1.79-3.08)	2.49 (1.90-3.26)	2.44 (1.86-3.20)	2.28 (1.73-2.99)	2.39 (1.83-3.12)	2.48 (1.89-3.25)	2.32 (1.73-3.11)
Age (continuous)		0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)

Table 3. Adjusted hazard ratios for migraine predicting depression, adjusting for various stressors, age, and sex

	Model 1 (n=7,339)	Model 2 (n=7,339)	Model 3 (n=6,840)	Model 4 (n=7,121)	Model 5 (n=7,176)	Model 6 (n=7,144)	Model 7 (n=7,127)	Model 8 (n=7,339)	Model 9 (n=6,387)
Migraine									
Yes	1.84 (1.38-2.45)	1.55 (1.15-2.08)	1.43 (1.06-1.92)	1.46 (1.08-1.98)	1.54 (1.14-2.08)	1.51 (1.11-2.05)	1.33 (0.98-1.79)	1.46 (1.07-1.99)	1.19 (0.86-1.66)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Childhood Trauma									
None			Reference						Reference
1			1.23 (0.92-1.64)						1.14 (0.84-1.55)
2+			2.36 (1.79-3.12)						1.89 (1.38-2.59)
Recent Marital Status Change									
Yes				0.91 (0.40-2.06)					0.78 (0.33-1.84)
No				Reference					Reference
Recent Unemployed									
Yes					1.52 (0.93-2.49)				1.16 (0.68-1.99)
No					Reference				Reference
Work Stress									
1st Quartile						Reference			Reference
2nd Quartile						0.64 (0.48-0.85)			0.70 (0.52-0.95)
3rd Quartile						0.69 (0.50-0.94)			0.76 (0.55-1.06)
4th Quartile						1.12 (0.84-1.51)			1.06 (0.77-1.48)
Chronic Stress									
1st Quartile							Reference		Reference
2nd Quartile							1.45 (1.06-2.00)		1.47 (1.03-2.08)
3rd Quartile							2.02 (1.50-2.73)		1.89 (1.37-2.62)
4th Quartile							2.93 (2.20-3.88)		2.49 (1.80-3.44)
Change in Social Support									
Yes								0.91 (0.69-1.20)	0.94 (0.71-1.23)
No								Reference	Reference
Sex									
Male		Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female		1.91 (1.52-2.39)	1.86 (1.49-2.34)	1.94 (1.55-2.44)	1.92 (1.53-2.41)	1.80 (1.43-2.27)	1.89 (1.50-2.37)	1.89 (1.50-2.39)	1.83 (1.43-2.34)
Age (continuous)		0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)

The Contribution of Stress to the Comorbidity of Migraine and Major Depression: Results from a Prospective Cohort Study

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The Contribution of Stress to the Comorbidity of Migraine and Major Depression: Results from a Prospective Cohort Study

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Abstract

Objectives: To assess how much the association between migraine and depression may be explained by various measures of stress.

Design: National Population Health Survey is a prospective cohort study representative of the Canadian population. Eight years of follow-up time were used in the present analyses.

Setting: Canadian adult population ages 18-64

Participants: 9,288 participants

Outcome: Incident migraine and major depression

Results: Adjusting for sex and age, depression was predictive of incident migraine (HR: 1.62; 95% CI: 1.03-2.53) and migraine was predictive of incident depression (HR: 1.55; 95% CI: 1.15-2.08). However, adjusting for each assessed stressor (childhood trauma, recent marital problems, recent unemployment, recent household financial problems, work stress, chronic stress, and change in social support) decreased this association, with chronic stress being a particularly strong predictor of outcomes. When adjusting for all stressors simultaneously, both associations were largely attenuated (depression-migraine HR: 1.30; 95% CI: 0.80-2.10; migraine-depression HR: 1.19; 95% CI: 0.86-1.66).

Conclusions: Much of the apparent association between migraine and depression may be explained by stress.

ARTICLE SUMMARY

Article Focus

- To understand how much and what kinds of stressors play a role in explaining the comorbidity seen between migraine and major depression

Key Messages

- Migraine headache and major depression each predict the other prospectively
- Stress, particularly chronic stress, appears to explain much of the association seen between migraine and major depression

Strengths and Limitations

- Large, representative, prospective cohort study
- Migraine was self-reported with only a single question

INTRODUCTION

Several studies support that migraine and psychopathologies, in particular major depression, often co-occur.[1-15] In a recent review of such comorbidities, Antonaci et al reported a meta-analysis of 12 studies, concluding that the odds ratio may be near 2.2 for major depression and migraine.[16] A limited number of prospective studies have examined the temporality of this association, largely concluding the predictive relationship is bidirectional (i.e., migraine status predicts depression onset and vice versa).[1, 2, 10] While the correlation has been well established, the mechanisms for this co-occurrence are less clear; causal paths may exist from one disorder to the other, and/or some shared common risk factor(s) (i.e., confounders) may cause both depression and migraine.

Migraine and depression indeed share several risk factors, and thus any perceived correlation between the two could potentially be due to this confounding. Prior research assessing their association has adjusted primarily for demographic variables, however some studies have separately studied other risk factors of a genetic and neurobiologic nature. Few studies, however, have focused on stress, a known risk factor for both migraine and depression. In Modgill and colleagues' analyses of the National Population Health Survey (NPHS), a representative longitudinal study of the Canadian population, childhood trauma attenuated the association between the two disorders, particularly for the direction of depression predicting migraine onset.[10] However, their analyses only looked at a limited number of stressors and did not attempt to address specifically how much different types of stressors may contribute to this association. A variety of stressors may confound the migraine-depression association, as many types have been found to be

risk factors for both disorders: e.g., childhood trauma,[10, 17] unemployment,[18, 19] chronic/repeated stress,[20, 21] etc.

In the current study, we extend upon Modgill et al's findings in the NPHS to assess how much the association between migraine and depression may be explained by various measures of stress, including a wide variety of prior and current stressors. We assess this association longitudinally and bidirectionally.

METHODS

Sample

The NPHS is a prospective, nationally representative study conducted by Statistics Canada that has followed a Canadian cohort since 1994/95. At study inception, individuals were randomly selected using a stratified two-stage sample design (n=17,276). The sample has been contacted every two years, with the most recent data collection in 2008/09.

For the purposes of this study, we restricted our sample to individuals aged 18 to 64 years in Cycle 4 (2000/01), with this assessment treated as "baseline" in the presented analyses. This serves two purposes: (1) as both migraine and depression assessments reflect current states rather than diagnostic histories, this allows us to use the first three assessments to construct a several-year history of each disorder prior to baseline; and (2) as some of the stressors were not assessed until this time (e.g., work stress, chronic stress) or could not be constructed without at least two assessments (e.g., change in social support, marital status, or employment), this allows a more complete analysis of the role of stressors in the migraine-depression comorbidity. Further information on our analytic sample is depicted in Figure 1.

Depression

Major depressive episodes are assessed using the Composite International Diagnostic Interview Short Form for Major Depression (CIDI-SFMD) at all eight cycles. The CIDI-SFMD inquires about symptoms of major depression, as defined by the

Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), during the preceding 12 months. Kessler and colleagues[22] showed that the CIDI-SF has 93% classification accuracy for major depressive episode when compared with the full-length CIDI. Individuals who endorse five or more symptoms during a single two-week period are considered to have a 90% probability of having major depression;[22] for the purposes of this study, such individuals will be considered as having major depression in that year.

Migraine

Migraine is assessed in a single diagnostic question at each assessment. In the first three assessments (1994/95; 1996/97; 1998/99), subjects were asked whether they currently were having migraine headaches that had been diagnosed by a health professional. In the subsequent five assessments (2000/01; 2002/03; 2004/05; 2006/07; 2008/09), subjects were asked whether they currently have migraine headaches. In these last five assessments, subjects were further asked about the timing of onset of the diagnosis.

Stressors

Using similar definitions as previous studies using NPHS data,[17] we defined several types of stressors: childhood trauma, recent marital problems, recent unemployment, recent household financial problems, work stress, chronic stress, and change in social support. Childhood trauma was assessed in Cycle 1 (1994/95) for those 18 or older at that time, and in Cycle 4 (2000/01) for the rest of our cohort. Subjects were asked about seven items of childhood trauma occurring prior to the individual turning 18: parental divorce, a lengthy hospital stay, prolonged parental unemployment, frequent parental alcohol or drug use and physical abuse. Childhood trauma was categorized as

none, one event, and two or more events. Three recent stressful life changes were defined: marital problems, recent unemployment, and household financial problems. Marital problems were defined by a change from reporting single, married, or partnered in Cycle 3 (1998/99) to divorced, widowed, or separated in Cycle 4 (2000/01). Recent unemployment was defined as being employed in Cycle 3 (1998/99) but reporting unemployment or not being in the labor force in Cycle 4 (2000/01). Household financial problems were defined as having a score above Statistic Canada's low income cut-off (LICO) in Cycle 3 (1998/99) followed by a score below the cut-off in Cycle 4 (2000/01). The LICO score takes into account the individual's income relative to the community in which an individual lives and the size of their household.[23, 24] Work stress was measured in Cycle 4 (2000/01) by 13 questions that assessed job security, autonomy, conflict and satisfaction;[24] the score was categorized by quartiles. Chronic stress was measured in Cycle 4 (2000/01) by 18 questions that assessed stress in one's personal life, focusing primarily on relationships and family strife;[24] this score was also broken into quartiles. Social support was measured by a 4-question scale in Cycles 3 and 4 (1998/99; 2000/01);[24] this score was dichotomized at the median, and change in social support was conceptualized as a change from high to low social support.

Statistical Analyses

We performed two sets of analyses. First, among those with no history of major depression (unweighted n=7,818), we assessed the onset of incident major depression comparing those with and without migraine at baseline; second, among those with no history of migraine (unweighted n=7,765), we assessed the onset of incident migraine comparing those with and without major depression at baseline. Cox Proportional

Hazards Models were fit, and hazards ratios (HR) and their 95% confidence intervals (CI) are presented. Models are presented as unadjusted; adjusting for sex and age; adjusting for sex, age, and each stress exposure individually; and adjusting for sex, age, and all stress exposures. Data analyses were completed using SAS 9.2 and SUDAAN 10.0.1. All estimates were weighted to adjust for unequal selection probabilities and cluster sampling; weights further adjust for attrition between the first and fourth cycle. Standard errors were calculated using the bootstrap method.

RESULTS

Demographic information is presented in **Table 1**. At baseline, 4.13, 9.13, and 1.33% of the sample reported current depression only, migraine only, and comorbid depression and migraine, respectively.

Models for depression status predicting incident migraine are presented in **Table 2**. Among non-migraineurs in Cycle 4 (2000/01), 5.52% developed migraine during the eight-year follow-up. The sex- and age-adjusted model suggested depression was predictive of incident migraine (HR: 1.62; 95% CI: 1.03-2.53). When adjusting further for stressors in separate models, estimates were further attenuated; adjusting for chronic stress attenuated the estimate the most (HR: 1.34; 95% CI: 0.84-2.13). When adjusting for all forms of stressors simultaneously, the depression-migraine estimate was attenuated to a HR of 1.30 (95% CI: 0.80-2.10).

Models for migraine status predicting incident depression are presented in **Table 3**. Among subjects who had not had a depression up through Cycle 4 (2000/01), 8.72% developed incident depression. Migraine status was predictive of incident depression in the age- and sex-adjusted model (HR: 1.55; 95% CI: 1.15-2.08). Adjusting for stressors in separate models attenuated this relationship, with adjustment for chronic stress affecting the estimate the most (HR: 1.33; 95% CI: 0.98-1.79). The fully adjusted model estimate for the migraine-depression HR was attenuated to 1.19 (95% CI: 0.86-1.66).

DISCUSSION

Without considering common causes or other explanations, these results align with earlier findings supporting a bidirectionality to a migraine-depression association: in crude analyses, migraine status predicted incident depression, and depression status predicted incident migraine. However, both directions of this relationship are largely explained by stressors that likely increase risk for both migraine and depression: adjusting for all measured forms of stress in these surveys attenuated the each estimate considerably (estimates decreased from 1.62 to 1.30, and 1.55 to 1.19) and the associations were no longer significant after adjustment. Implications for research as well as clinical and public health practice are discussed.

Importantly, all stressors studied here did attenuate the results, suggesting that any form of stress may be an important common cause to consider when studying migraine and depression. This finding follows from prior research that supports both acute and chronic forms of stress as being confounders, since these have been shown to predict depression and migraine.[10, 17-21] The present study suggests that prior studies that these stressors collectively explain much of the perceived migraine-depression association; research that does not account for these common causes when studying depression and migraine may be presenting misleading estimates. The perceived migraine-depression associations presented in many prior studies may be largely explained by unmeasured confounding by such types of stressors. The magnitude of confounding due to each specific stressor is dependent on several factors, including the strength of the covariate-exposure association, the strength of the covariate-outcome association, and the prevalence of the covariate. Our measure of chronic stress was strongly predictive of both

migraine and depression onset, as well as associated with these disorders at baseline, and thus was the strongest risk factor considered in the present analyses. On the other hand, recent changes in employment and marital status were relatively rare life events, and were not strongly predictive of these disorders, so the magnitude of attenuation when considering each of these variables was minor. Optimally, future studies of migraine and depression would assess all potential confounders; as this is not always feasible, investigators may consider prioritizing assessing chronic stress over some of these other stressors, and accompany results with sensitivity or bias analyses for any stressors that remained unmeasured.

Our finding that chronic stress was the strongest stress-related risk factor fits into the broader context of research suggesting that chronic stress may be causative of various types of chronic pain and major depression. In disentangling the relationship between depression, chronic stress, and chronic pain such as fibromyalgia, its been proposed that chronic stress may lead to dysfunction in the hypothalamic-pituitary-adrenal axis, which in turn could lead to both depression and some forms of chronic pain.[25] Research specific to stress and migraine supports this biological theory.[26] Notably, childhood trauma was a strong risk factor in migraine predicting depression; as many of the types of trauma assessed were chronic in nature, this aligns with the finding that perhaps chronic forms of stress are especially potent common causes of migraine and depression.

Although certainly some of the crude association between depression and migraine may still be explained by genetics, other common causes, and/or biological pathways between the two disorders, the current findings suggest interesting considerations when developing future intervention strategies. Given the possibility of a

biological mechanism between these two disorders, much research attention has been focused on the efficacy of antidepressant medications on preventing and managing migraine, with mixed success.[27-29] However, the current study suggests that perhaps a primary strategy could target reducing stress, particularly chronic stress, as this may both reduce the burden of the index disorder as well as potentially prevent the second condition from occurring. Indeed, there have been studies showing that various behavioural or stress management therapies (e.g., Cognitive-Behavioral Therapy) are effective treatments for migraine, supporting one aspect of this hypothesis.[30-32] Given how much chronic stress and other stressors seem to explain the comorbidity, such a strategy may have the potential for reducing this comorbidity burden on a larger scale than some of these other postulated pharmacological strategies, although further research actually comparing such treatment strategies would be needed. Utilizing a stress-reducing strategy to address this comorbidity assumes that stress is (directly or indirectly) causative of both disorders, while it is possible that stress is a risk factor through associations with a common cause.

The study has numerous strengths. This is one of only a few studies to prospectively assess the migraine-depression comorbidity bidirectionally,[1, 2, 10] and extends these previous findings by examining whether a rich assortment of widely-used stress measures explained the associations found. The nationally-representative nature of the study aids the generalizability of these findings, and the sample size and length of follow-up are exceptional.

However, certain limitations warrant consideration. Migraine was assessed as only a single, self-reported question at each cycle. Self-reported symptom-based

assessments do generally report a higher prevalence than doctor diagnoses;[33] the assessment in the NPHS inquires about diagnosis by a health professional which may offset some of this over-reporting, but certainly misclassification may still be an issue. Specifically, self-report may be further inflated in depressed individuals, which may actually contribute to some overestimation in our associations. While the measure of major depression (CIDI-SFMD) has demonstrated psychometric properties,[22, 34, 35] the 12-month diagnosis (which thus does not cover the 2 years between each study assessment) hinders inference about history of major depression, possible episodes unmeasured in the gap years of the study, and actual timing of onset of the disorder; subjects who have less frequent depressive episodes or episodes that are shorter in duration would be less likely to be measured accurately. However, by using an interim cycle as "baseline", we were able to construct over a half-decade profile of subjects' "history" of major depression to diminish the issue regarding assessing history. Finally, we did not have complete follow-up for all subjects. Weighting was used to correct for attrition between Cycles 1 and 4. From Cycle 4 through 8 the majority of subjects were assessed eight years later (see Figure 1), and follow-up duration was not associated with migraine or depression status at baseline. Follow-up duration, however, was associated with age and a few stressors (greater chronic stress, recent unemployment, and recent divorce were associated with shorter follow-up; p's<0.05); however, as stress likely predicts higher levels of the outcome disorders, its likely this implies that some subjects were censored prior to onset of the outcome, meaning that stress would explain even more of the association measured had complete follow-up occurred.

These analyses highlight considerations for future research. These analyses represent a rich assortment of stressors, but several other stressors may also merit examination, e.g., childhood sexual abuse, acute recent traumas such as injury or illness, etc. Further, as some of the stressors were only assessed in one or two cycles, we were not able to fully address the time-varying nature of the relationships between stress and these episodic conditions. Given that we found recent and prior stress to be relevant in this comorbidity, future research may wish to more closely examine the time-varying relationship between stress and these two conditions individually and comorbidly. Specifically, while stress is a risk factor for both disorders, it may also be caused by each disorder, and thus assessing temporal relationships using models that account for time-varying confounding appropriately (e.g., marginal structural models), may highlight the relationship between these variables further.

Understanding the causal mechanisms underlying the migraine-depression comorbidity may have a major public health impact. Major depression is a chief cause of disability worldwide,[36] estimated by the World Health Organization to become the second leading cause of disease burden by the year 2020.[37] Meanwhile, migraine affects 11% of the adult population, and when combined with other headache disorders also makes it into the top ten causes of disability by World Health Organization estimates.[38] Moreover, studies suggest that the disability and burden of these disorders may be compounded when present together;[5] disease severity appears greater when these disorders are comorbid, e.g., frequency and duration of migraine attacks have a significant association with psychiatric comorbidity.[39] Migraine patients with a psychiatric disorder report generally lower quality of life than other migraine patients;[8]

in parallel, depression patients who report migraine also report poorer quality of life compared to other depression patients.[40] As such, implementation of effective stress-management strategies for migraineurs and those suffering from depression (as well as similar strategies to prevent the index disorder onset) may have major implications for prevention and intervention strategies that may lower the societal costs and burdens of both disorders.

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COMPETING INTERESTS

None declared

AUTHOR CONTRIBUTIONS

SS and IC conceived and designed the study and interpreted the results. SS, YZ and MW performed the data analysis. SS wrote the manuscript. All authors critically reviewed the final manuscript.

Table 1. Sample Characteristics Ages 18-64, % (SE)

Variable	Unweighted N	% (SE)
N	9,342	
Sex		
Male	4,986	50.31 (0.17)
Female	4,356	49.69 (0.17)
Age, mean (range)		40.77 (18-64)
Baseline Migraine/Depression Comorbidity		
None	7,619	85.41 (0.49)
Depression Only	404	4.13 (0.29)
Migraine Only	839	9.13 (0.40)
Depression and Migraine	124	1.33 (0.17)
Childhood Trauma		
0	4,194	49.61 (0.74)
1	2,265	25.82 (0.64)
2+	2,274	24.57 (0.65)
Recent Marital Change to Divorced, Separated, or Widowed		
Yes	214	2.47 (0.23)
No	8,781	97.53 (0.23)
Recent Unemployment		
Yes	394	4.34 (0.32)
No	8,670	95.66 (0.32)
Recent Change in Social Support		
Yes	1,359	16.76 (0.60)
No	6,961	83.24 (0.60)
Years of Follow-Up		
Median		7.30
IQR		6.29-7.67

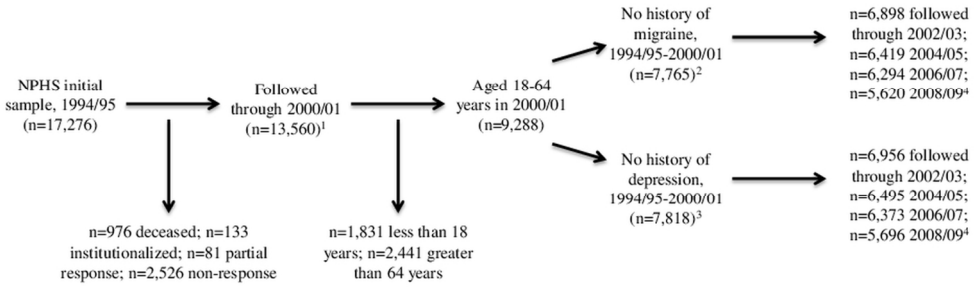
Table 2. Adjusted hazard ratios for depression predicting migraine, adjusting for various stressors, age, and sex

	Model 1 (n=7,076)	Model 2 (n=7,076)	Model 3 (n=6,678)	Model 4 (n=6,868)	Model 5 (n=6,953)	Model 6 (n=7,064)	Model 7 (n=7,044)	Model 8 (n=7,076)	Model 9 (n=6,339)
Depression									
Yes	1.85 (1.20-2.85)	1.62 (1.03-2.53)	1.59 (1.03-2.46)	1.56 (0.98-2.47)	1.61 (1.02-2.53)	1.52 (0.97-2.38)	1.34 (0.84-2.13)	1.61 (1.02-2.54)	1.30 (0.80-2.10)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Childhood Trauma									
None			Reference						Reference
1			0.95 (0.66-1.37)						0.90 (0.60-1.33)
2+			1.34 (1.00-1.79)						1.09 (0.79-1.51)
Recent Marital Status Change									
Yes				1.54 (0.82-2.90)					1.28 (0.59-2.75)
No				Reference					Reference
Recent Unemployment									
Yes					1.00 (0.44-2.30)				0.72 (0.29-1.78)
No					Reference				Reference
Work Stress									
1st Quartile						Reference			Reference
2nd Quartile						0.63 (0.42-0.95)			0.61 (0.39-0.95)
3rd Quartile						0.66 (0.45-0.96)			0.63 (0.41-0.96)
4th Quartile						0.89 (0.61-1.31)			0.81 (0.52-1.27)
Chronic Stress									
1st Quartile							Reference		Reference
2nd Quartile							0.91 (0.59-1.40)		0.99 (0.63-1.56)
3rd Quartile							1.58 (1.11-2.25)		1.64 (1.12-2.41)
4th Quartile							1.76 (1.22-2.53)		1.68 (1.08-2.61)
Change in Social Support									
Yes								0.77 (0.54-1.11)	0.84 (0.58-1.21)
No								Reference	Refererence
Sex									
Male		Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female		2.39 (1.83-3.12)	2.34 (1.79-3.08)	2.49 (1.90-3.26)	2.44 (1.86-3.20)	2.28 (1.73-2.99)	2.39 (1.83-3.12)	2.48 (1.89-3.25)	2.32 (1.73-3.11)
Age (continuous)		0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)

Table 3. Adjusted hazard ratios for migraine predicting depression, adjusting for various stressors, age, and sex

	Model 1 (n=7,339)	Model 2 (n=7,339)	Model 3 (n=6,840)	Model 4 (n=7,121)	Model 5 (n=7,176)	Model 6 (n=7,144)	Model 7 (n=7,127)	Model 8 (n=7,339)	Model 9 (n=6,387)
Migraine									
Yes	1.84 (1.38-2.45)	1.55 (1.15-2.08)	1.43 (1.06-1.92)	1.46 (1.08-1.98)	1.54 (1.14-2.08)	1.51 (1.11-2.05)	1.33 (0.98-1.79)	1.46 (1.07-1.99)	1.19 (0.86-1.66)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Childhood Trauma									
None			Reference						Reference
1			1.23 (0.92-1.64)						1.14 (0.84-1.55)
2+			2.36 (1.79-3.12)						1.89 (1.38-2.59)
Recent Marital Status Change									
Yes				0.91 (0.40-2.06)					0.78 (0.33-1.84)
No				Reference					Reference
Recent Unemployed									
Yes					1.52 (0.93-2.49)				1.16 (0.68-1.99)
No					Reference				Reference
Work Stress									
1st Quartile						Reference			Reference
2nd Quartile						0.64 (0.48-0.85)			0.70 (0.52-0.95)
3rd Quartile						0.69 (0.50-0.94)			0.76 (0.55-1.06)
4th Quartile						1.12 (0.84-1.51)			1.06 (0.77-1.48)
Chronic Stress									
1st Quartile							Reference		Reference
2nd Quartile							1.45 (1.06-2.00)		1.47 (1.03-2.08)
3rd Quartile							2.02 (1.50-2.73)		1.89 (1.37-2.62)
4th Quartile							2.93 (2.20-3.88)		2.49 (1.80-3.44)
Change in Social Support									
Yes								0.91 (0.69-1.20)	0.94 (0.71-1.23)
No								Reference	Reference
Sex									
Male		Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female		1.91 (1.52-2.39)	1.86 (1.49-2.34)	1.94 (1.55-2.44)	1.92 (1.53-2.41)	1.80 (1.43-2.27)	1.89 (1.50-2.37)	1.89 (1.50-2.39)	1.83 (1.43-2.34)
Age (continuous)		0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)

Figure 1. Flow diagram of sample inclusion and exclusion during study period



1. Analyses incorporate weights to account for attrition between 1994/95 and 2000/01 as well as unequal selection probabilities and cluster sampling from the initial study design.
2. Analyses of depression status in 2000/01 predicting migraine onset are performed on this sub-cohort.
3. Analyses of migraine status in 2000/01 predicting depression onset are performed on this sub-cohort.
4. Median follow-up time of participants aged 18-64 years in 2000/01 was 7.30 further years (IQR = 6.29-7.67).

119x90mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Check?	Recommendation
Title and abstract	x	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	x	Explain the scientific background and rationale for the investigation being reported
Objectives	x	State specific objectives, including any prespecified hypotheses
Methods		
Study design	x	Present key elements of study design early in the paper
Setting	x	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	x	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	x	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	x	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	x	Describe any efforts to address potential sources of bias
Study size	x	Explain how the study size was arrived at
Quantitative variables	x	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	x	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	x	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	x	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	x	Report numbers of outcome events or summary measures over

		time
Main results	x	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	x	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	x	Summarise key results with reference to study objectives
Limitations	x	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	x	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	x	Discuss the generalisability (external validity) of the study results
Other information		
Funding	x	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Number of References: 40

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Figures: 1

The Contribution of Stress to the Comorbidity of Migraine and Major Depression: Results from a Prospective Cohort Study

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Keywords: migraine, major depression, stress, trauma

Abstract

Objectives: To assess how much the association between migraine and depression may be explained by various measures of stress.

Design: National Population Health Survey is a prospective cohort study representative of the Canadian population. Eight years of follow-up time were used in the present analyses.

Setting: Canadian adult population ages 18-64

Participants: 9,288 participants

Outcome: Incident migraine and major depression

Results: Adjusting for sex and age, depression was predictive of incident migraine (HR: 1.62; 95% CI: 1.03-2.53) and migraine was predictive of incident depression (HR: 1.55; 95% CI: 1.15-2.08). However, adjusting for each assessed stressor (childhood trauma, recent marital problems, recent unemployment, recent household financial problems, work stress, chronic stress, and change in social support) decreased this association, with chronic stress being a particularly strong predictor of outcomes. When adjusting for all stressors simultaneously, both associations were largely attenuated (depression-migraine HR: 1.30; 95% CI: 0.80-2.10; migraine-depression HR: 1.19; 95% CI: 0.86-1.66).

Conclusions: Much of the apparent association between migraine and depression may be explained by stress.

ARTICLE SUMMARY

Article Focus

- To understand how much and what kinds of stressors play a role in explaining the comorbidity seen between migraine and major depression

Key Messages

- Migraine headache and major depression each predict the other prospectively
- Stress, particularly chronic stress, appears to explain much of the association seen between migraine and major depression

Strengths and Limitations

- Large, representative, prospective cohort study
- Migraine was self-reported with only a single question

INTRODUCTION

Several studies support that migraine and psychopathologies, in particular major depression, often co-occur.[1-15] In a recent review of such comorbidities, Antonaci et al reported a meta-analysis of 12 studies, concluding that the odds ratio may be near 2.2 for major depression and migraine.[16] A limited number of prospective studies have examined the temporality of this association, largely concluding the predictive relationship is bidirectional (i.e., migraine status predicts depression onset and vice versa).[1, 2, 10] While the correlation has been well established, the mechanisms for this co-occurrence are less clear; causal paths may exist from one disorder to the other, and/or some shared common risk factor(s) (i.e., confounders) may cause both depression and migraine.

Migraine and depression indeed share several risk factors, and thus any perceived correlation between the two could potentially be due to this confounding. Prior research assessing their association has adjusted primarily for demographic variables, however some studies have separately studied other risk factors of a genetic and neurobiologic nature. Few studies, however, have focused on stress, a known risk factor for both migraine and depression. In Modgill and colleagues' analyses of the National Population Health Survey (NPHS), a representative longitudinal study of the Canadian population, childhood trauma attenuated the association between the two disorders, particularly for the direction of depression predicting migraine onset.[10] However, their analyses only looked at a limited number of stressors and did not attempt to address specifically how much different types of stressors may contribute to this association. A variety of stressors may confound the migraine-depression association, as many types have been found to be

risk factors for both disorders: e.g., childhood trauma,[10, 17] unemployment,[18, 19] chronic/repeated stress,[20, 21] etc.

In the current study, we extend upon Modgill et al's findings in the NPHS to assess how much the association between migraine and depression may be explained by various measures of stress, including a wide variety of prior and current stressors. We assess this association longitudinally and bidirectionally.

METHODS

Sample

The NPHS is a prospective, nationally representative study conducted by Statistics Canada that has followed a Canadian cohort since 1994/95. At study inception, individuals were randomly selected using a stratified two-stage sample design (n=17,276). The sample has been contacted every two years, with the most recent data collection in 2008/09.

For the purposes of this study, we restricted our sample to individuals aged 18 to 64 years in Cycle 4 (2000/01), with this assessment treated as "baseline" in the presented analyses. This serves two purposes: (1) as both migraine and depression assessments reflect current states rather than diagnostic histories, this allows us to use the first three assessments to construct a several-year history of each disorder prior to baseline; and (2) as some of the stressors were not assessed until this time (e.g., work stress, chronic stress) or could not be constructed without at least two assessments (e.g., change in social support, marital status, or employment), this allows a more complete analysis of the role of stressors in the migraine-depression comorbidity. Further information on our analytic sample is depicted in Figure 1.

Depression

Major depressive episodes are assessed using the Composite International Diagnostic Interview Short Form for Major Depression (CIDI-SFMD) at all eight cycles. The CIDI-SFMD inquires about symptoms of major depression, as defined by the

Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), during the preceding 12 months. Kessler and colleagues[22] showed that the CIDI-SF has 93% classification accuracy for major depressive episode when compared with the full-length CIDI. Individuals who endorse five or more symptoms during a single two-week period are considered to have a 90% probability of having major depression;[22] for the purposes of this study, such individuals will be considered as having major depression in that year.

Migraine

Migraine is assessed in a single diagnostic question at each assessment. In the first three assessments (1994/95; 1996/97; 1998/99), subjects were asked whether they currently were having migraine headaches that had been diagnosed by a health professional. In the subsequent five assessments (2000/01; 2002/03; 2004/05; 2006/07; 2008/09), subjects were asked whether they currently have migraine headaches. In these last five assessments, subjects were further asked about the timing of onset of the diagnosis.

Stressors

Using similar definitions as previous studies using NPHS data,[17] we defined several types of stressors: childhood trauma, recent marital problems, recent unemployment, recent household financial problems, work stress, chronic stress, and change in social support. Childhood trauma was assessed in Cycle 1 (1994/95) for those 18 or older at that time, and in Cycle 4 (2000/01) for the rest of our cohort. Subjects were asked about seven items of childhood trauma occurring prior to the individual turning 18: parental divorce, a lengthy hospital stay, prolonged parental unemployment, frequent parental alcohol or drug use and physical abuse. Childhood trauma was categorized as

none, one event, and two or more events. Three recent stressful life changes were defined: marital problems, recent unemployment, and household financial problems. Marital problems were defined by a change from reporting single, married, or partnered in Cycle 3 (1998/99) to divorced, widowed, or separated in Cycle 4 (2000/01). Recent unemployment was defined as being employed in Cycle 3 (1998/99) but reporting unemployment or not being in the labor force in Cycle 4 (2000/01). Household financial problems were defined as having a score above Statistic Canada's low income cut-off (LICO) in Cycle 3 (1998/99) followed by a score below the cut-off in Cycle 4 (2000/01). The LICO score takes into account the individual's income relative to the community in which an individual lives and the size of their household.[23, 24] Work stress was measured in Cycle 4 (2000/01) by 13 questions that assessed job security, autonomy, conflict and satisfaction;[24] the score was categorized by quartiles. Chronic stress was measured in Cycle 4 (2000/01) by 18 questions that assessed stress in one's personal life, focusing primarily on relationships and family strife;[24] this score was also broken into quartiles. Social support was measured by a 4-question scale in Cycles 3 and 4 (1998/99; 2000/01);[24] this score was dichotomized at the median, and change in social support was conceptualized as a change from high to low social support.

Statistical Analyses

We performed two sets of analyses. First, among those with no history of major depression (unweighted n=7,818), we assessed the onset of incident major depression comparing those with and without migraine at baseline; second, among those with no history of migraine (unweighted n=7,765), we assessed the onset of incident migraine comparing those with and without major depression at baseline. Cox Proportional

Hazards Models were fit, and hazards ratios (HR) and their 95% confidence intervals (CI) are presented. Models are presented as unadjusted; adjusting for sex and age; adjusting for sex, age, and each stress exposure individually; and adjusting for sex, age, and all stress exposures. Data analyses were completed using SAS 9.2 and SUDAAN 10.0.1. All estimates were weighted to adjust for unequal selection probabilities and cluster sampling; weights further adjust for attrition between the first and fourth cycle. Standard errors were calculated using the bootstrap method.

RESULTS

Demographic information is presented in **Table 1**. At baseline, 4.13, 9.13, and 1.33% of the sample reported current depression only, migraine only, and comorbid depression and migraine, respectively.

Models for depression status predicting incident migraine are presented in **Table 2**. Among non-migraineurs in Cycle 4 (2000/01), 5.52% developed migraine during the eight-year follow-up. The sex- and age-adjusted model suggested depression was predictive of incident migraine (HR: 1.62; 95% CI: 1.03-2.53). When adjusting further for stressors in separate models, estimates were further attenuated; adjusting for chronic stress attenuated the estimate the most (HR: 1.34; 95% CI: 0.84-2.13). When adjusting for all forms of stressors simultaneously, the depression-migraine estimate was attenuated to a HR of 1.30 (95% CI: 0.80-2.10).

Models for migraine status predicting incident depression are presented in **Table 3**. Among subjects who had not had a depression up through Cycle 4 (2000/01), 8.72% developed incident depression. Migraine status was predictive of incident depression in the age- and sex-adjusted model (HR: 1.55; 95% CI: 1.15-2.08). Adjusting for stressors in separate models attenuated this relationship, with adjustment for chronic stress affecting the estimate the most (HR: 1.33; 95% CI: 0.98-1.79). The fully adjusted model estimate for the migraine-depression HR was attenuated to 1.19 (95% CI: 0.86-1.66).

DISCUSSION

Without considering common causes or other explanations, these results align with earlier findings supporting a bidirectionality to a migraine-depression association: in crude analyses, migraine status predicted incident depression, and depression status predicted incident migraine. However, both directions of this relationship are largely explained by stressors that likely increase risk for both migraine and depression: adjusting for all measured forms of stress in these surveys attenuated the each estimate considerably (estimates decreased from 1.62 to 1.30, and 1.55 to 1.19) and the associations were no longer significant after adjustment. Implications for research as well as clinical and public health practice are discussed.

Importantly, all stressors studied here did attenuate the results, suggesting that any form of stress may be an important common cause to consider when studying migraine and depression. This finding follows from prior research that supports both acute and chronic forms of stress as being confounders, since these have been shown to predict depression and migraine.[10, 17-21] The present study suggests that prior studies that these stressors collectively explain much of the perceived migraine-depression association; research that does not account for these common causes when studying depression and migraine may be presenting misleading estimates. The perceived migraine-depression associations presented in many prior studies may be largely explained by unmeasured confounding by such types of stressors. The magnitude of confounding due to each specific stressor is dependent on several factors, including the strength of the covariate-exposure association, the strength of the covariate-outcome association, and the prevalence of the covariate. Our measure of chronic stress was strongly predictive of both

migraine and depression onset, as well as associated with these disorders at baseline, and thus was the strongest risk factor considered in the present analyses. On the other hand, recent changes in employment and marital status were relatively rare life events, and were not strongly predictive of these disorders, so the magnitude of attenuation when considering each of these variables was minor. Optimally, future studies of migraine and depression would assess all potential confounders; as this is not always feasible, investigators may consider prioritizing assessing chronic stress over some of these other stressors, and accompany results with sensitivity or bias analyses for any stressors that remained unmeasured.

Our finding that chronic stress was the strongest stress-related risk factor fits into the broader context of research suggesting that chronic stress may be causative of various types of chronic pain and major depression. In disentangling the relationship between depression, chronic stress, and chronic pain such as fibromyalgia, its been proposed that chronic stress may lead to dysfunction in the hypothalamic-pituitary-adrenal axis, which in turn could lead to both depression and some forms of chronic pain.[25] Research specific to stress and migraine supports this biological theory.[26] Notably, childhood trauma was a strong risk factor in migraine predicting depression; as many of the types of trauma assessed were chronic in nature, this aligns with the finding that perhaps chronic forms of stress are especially potent common causes of migraine and depression.

Although certainly some of the crude association between depression and migraine may still be explained by genetics, other common causes, and/or biological pathways between the two disorders, the current findings suggest interesting considerations when developing future intervention strategies. Given the possibility of a

biological mechanism between these two disorders, much research attention has been focused on the efficacy of antidepressant medications on preventing and managing migraine, with mixed success.[27-29] However, the current study suggests that perhaps a primary strategy could target reducing stress, particularly chronic stress, as this may both reduce the burden of the index disorder as well as potentially prevent the second condition from occurring. Indeed, there have been studies showing that various behavioural or stress management therapies (e.g., Cognitive-Behavioral Therapy) are effective treatments for migraine, supporting one aspect of this hypothesis.[30-32] Given how much chronic stress and other stressors seem to explain the comorbidity, such a strategy may have the potential for reducing this comorbidity burden on a larger scale than some of these other postulated pharmacological strategies, although further research actually comparing such treatment strategies would be needed. Utilizing a stress-reducing strategy to address this comorbidity assumes that stress is (directly or indirectly) causative of both disorders, while it is possible that stress is a risk factor through associations with a common cause.

The study has numerous strengths. This is one of only a few studies to prospectively assess the migraine-depression comorbidity bidirectionally,[1, 2, 10] and extends these previous findings by examining whether a rich assortment of widely-used stress measures explained the associations found. The nationally-representative nature of the study aids the generalizability of these findings, and the sample size and length of follow-up are exceptional.

However, certain limitations warrant consideration. Migraine was assessed as only a single, self-reported question at each cycle. Self-reported symptom-based

assessments do generally report a higher prevalence than doctor diagnoses;[33] the assessment in the NPHS inquires about diagnosis by a health professional which may offset some of this over-reporting, but certainly misclassification may still be an issue. Specifically, self-report may be further inflated in depressed individuals, which may actually contribute to some overestimation in our associations. While the measure of major depression (CIDI-SFMD) has demonstrated psychometric properties,[22, 34, 35] the 12-month diagnosis (which thus does not cover the 2 years between each study assessment) hinders inference about history of major depression, possible episodes unmeasured in the gap years of the study, and actual timing of onset of the disorder; subjects who have less frequent depressive episodes or episodes that are shorter in duration would be less likely to be measured accurately. However, by using an interim cycle as "baseline", we were able to construct over a half-decade profile of subjects' "history" of major depression to diminish the issue regarding assessing history. Finally, we did not have complete follow-up for all subjects. Weighting was used to correct for attrition between Cycles 1 and 4. From Cycle 4 through 8 the majority of subjects were assessed eight years later (see Figure 1), and follow-up duration was not associated with migraine or depression status at baseline. Follow-up duration, however, was associated with age and a few stressors (greater chronic stress, recent unemployment, and recent divorce were associated with shorter follow-up; p's<0.05); however, as stress likely predicts higher levels of the outcome disorders, its likely this implies that some subjects were censored prior to onset of the outcome, meaning that stress would explain even more of the association measured had complete follow-up occurred.

These analyses highlight considerations for future research. These analyses represent a rich assortment of stressors, but several other stressors may also merit examination, e.g., childhood sexual abuse, acute recent traumas such as injury or illness, etc. Further, as some of the stressors were only assessed in one or two cycles, we were not able to fully address the time-varying nature of the relationships between stress and these episodic conditions. Given that we found recent and prior stress to be relevant in this comorbidity, future research may wish to more closely examine the time-varying relationship between stress and these two conditions individually and comorbidly. Specifically, while stress is a risk factor for both disorders, it may also be caused by each disorder, and thus assessing temporal relationships using models that account for time-varying confounding appropriately (e.g., marginal structural models), may highlight the relationship between these variables further.

Understanding the causal mechanisms underlying the migraine-depression comorbidity may have a major public health impact. Major depression is a chief cause of disability worldwide,[36] estimated by the World Health Organization to become the second leading cause of disease burden by the year 2020.[37] Meanwhile, migraine affects 11% of the adult population, and when combined with other headache disorders also makes it into the top ten causes of disability by World Health Organization estimates.[38] Moreover, studies suggest that the disability and burden of these disorders may be compounded when present together;[5] disease severity appears greater when these disorders are comorbid, e.g., frequency and duration of migraine attacks have a significant association with psychiatric comorbidity.[39] Migraine patients with a psychiatric disorder report generally lower quality of life than other migraine patients;[8]

in parallel, depression patients who report migraine also report poorer quality of life compared to other depression patients.[40] As such, implementation of effective stress-management strategies for migraineurs and those suffering from depression (as well as similar strategies to prevent the index disorder onset) may have major implications for prevention and intervention strategies that may lower the societal costs and burdens of both disorders.

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COMPETING INTERESTS

None declared

AUTHOR CONTRIBUTIONS

SS and IC conceived and designed the study and interpreted the results. SS, YZ and MW performed the data analysis. SS wrote the manuscript. All authors critically reviewed the manuscript.

Table 1. Sample Characteristics Ages 18-64, % (SE)

Variable	Unweighted N	% (SE)
N	9,342	
Sex		
Male	4,986	50.31 (0.17)
Female	4,356	49.69 (0.17)
Age, mean (range)		40.77 (18-64)
Baseline Migraine/Depression Comorbidity		
None	7,619	85.41 (0.49)
Depression Only	404	4.13 (0.29)
Migraine Only	839	9.13 (0.40)
Depression and Migraine	124	1.33 (0.17)
Childhood Trauma		
0	4,194	49.61 (0.74)
1	2,265	25.82 (0.64)
2+	2,274	24.57 (0.65)
Recent Marital Change to Divorced, Separated, or Widowed		
Yes	214	2.47 (0.23)
No	8,781	97.53 (0.23)
Recent Unemployment		
Yes	394	4.34 (0.32)
No	8,670	95.66 (0.32)
Recent Change in Social Support		
Yes	1,359	16.76 (0.60)
No	6,961	83.24 (0.60)
Years of Follow-Up		
Median		7.30
IQR		6.29-7.67

Table 2. Adjusted hazard ratios for depression predicting migraine, adjusting for various stressors, age, and sex

	Model 1 (n=7,076)	Model 2 (n=7,076)	Model 3 (n=6,678)	Model 4 (n=6,868)	Model 5 (n=6,953)	Model 6 (n=7,064)	Model 7 (n=7,044)	Model 8 (n=7,076)	Model 9 (n=6,339)
Depression									
Yes	1.85 (1.20-2.85)	1.62 (1.03-2.53)	1.59 (1.03-2.46)	1.56 (0.98-2.47)	1.61 (1.02-2.53)	1.52 (0.97-2.38)	1.34 (0.84-2.13)	1.61 (1.02-2.54)	1.30 (0.80-2.10)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Childhood Trauma									
None			Reference						Reference
1			0.95 (0.66-1.37)						0.90 (0.60-1.33)
2+			1.34 (1.00-1.79)						1.09 (0.79-1.51)
Recent Marital Status Change									
Yes				1.54 (0.82-2.90)					1.28 (0.59-2.75)
No				Reference					Reference
Recent Unemployment									
Yes					1.00 (0.44-2.30)				0.72 (0.29-1.78)
No					Reference				Reference
Work Stress									
1st Quartile						Reference			Reference
2nd Quartile						0.63 (0.42-0.95)			0.61 (0.39-0.95)
3rd Quartile						0.66 (0.45-0.96)			0.63 (0.41-0.96)
4th Quartile						0.89 (0.61-1.31)			0.81 (0.52-1.27)
Chronic Stress									
1st Quartile							Reference		Reference
2nd Quartile							0.91 (0.59-1.40)		0.99 (0.63-1.56)
3rd Quartile							1.58 (1.11-2.25)		1.64 (1.12-2.41)
4th Quartile							1.76 (1.22-2.53)		1.68 (1.08-2.61)
Change in Social Support									
Yes								0.77 (0.54-1.11)	0.84 (0.58-1.21)
No								Reference	Refererence
Sex									
Male		Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female		2.39 (1.83-3.12)	2.34 (1.79-3.08)	2.49 (1.90-3.26)	2.44 (1.86-3.20)	2.28 (1.73-2.99)	2.39 (1.83-3.12)	2.48 (1.89-3.25)	2.32 (1.73-3.11)
Age (continuous)		0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)

Table 3. Adjusted hazard ratios for migraine predicting depression, adjusting for various stressors, age, and sex

	Model 1 (n=7,339)	Model 2 (n=7,339)	Model 3 (n=6,840)	Model 4 (n=7,121)	Model 5 (n=7,176)	Model 6 (n=7,144)	Model 7 (n=7,127)	Model 8 (n=7,339)	Model 9 (n=6,387)
Migraine									
Yes	1.84 (1.38-2.45)	1.55 (1.15-2.08)	1.43 (1.06-1.92)	1.46 (1.08-1.98)	1.54 (1.14-2.08)	1.51 (1.11-2.05)	1.33 (0.98-1.79)	1.46 (1.07-1.99)	1.19 (0.86-1.66)
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Childhood Trauma									
None			Reference						Reference
1			1.23 (0.92-1.64)						1.14 (0.84-1.55)
2+			2.36 (1.79-3.12)						1.89 (1.38-2.59)
Recent Marital Status Change									
Yes				0.91 (0.40-2.06)					0.78 (0.33-1.84)
No				Reference					Reference
Recent Unemployed									
Yes					1.52 (0.93-2.49)				1.16 (0.68-1.99)
No					Reference				Reference
Work Stress									
1st Quartile						Reference			Reference
2nd Quartile						0.64 (0.48-0.85)			0.70 (0.52-0.95)
3rd Quartile						0.69 (0.50-0.94)			0.76 (0.55-1.06)
4th Quartile						1.12 (0.84-1.51)			1.06 (0.77-1.48)
Chronic Stress									
1st Quartile							Reference		Reference
2nd Quartile							1.45 (1.06-2.00)		1.47 (1.03-2.08)
3rd Quartile							2.02 (1.50-2.73)		1.89 (1.37-2.62)
4th Quartile							2.93 (2.20-3.88)		2.49 (1.80-3.44)
Change in Social Support									
Yes								0.91 (0.69-1.20)	0.94 (0.71-1.23)
No								Reference	Reference
Sex									
Male		Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female		1.91 (1.52-2.39)	1.86 (1.49-2.34)	1.94 (1.55-2.44)	1.92 (1.53-2.41)	1.80 (1.43-2.27)	1.89 (1.50-2.37)	1.89 (1.50-2.39)	1.83 (1.43-2.34)
Age (continuous)		0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)