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Investigating the Association between Migraine and Major Depression

A Retrospective Cohort Study

by

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A THESIS

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Abstract

Population-based cross-sectional studies have consistently reported an association between migraine and depression. However, longitudinal studies about their bidirectional association are inconsistent. This retrospective cohort study used 12 years of follow-up data from the Canadian National Population Health Survey (15,254 respondents, age >12). Stratified analysis, logistic regression, and proportional hazard modeling were used to quantify the effect of migraine on subsequent major depressive episodes (MDE) status and vice versa. After adjusting for sex, age, and other chronic health conditions, respondents with migraine were 60% more likely (HR 1.6, 95% CI 1.3-1.9) to develop MDE compared to those without migraine. Similarly adjusting for sex and age, respondents with MDE were 40% more likely (HR 1.4, 95% CI 1.0-1.9) to develop migraine compared to those without MDE. However, this association disappears after adjustment for stress and childhood trauma. Future research should seek to illuminate the mechanisms underlying the association between migraine and MDE.

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Dedication

Dedicated to my mother Pratibha, and my sister Arti, forever the brightest souls in my life.

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List of Symbols, Abbreviations, and Nomenclature

Symbol	Definition
BDI-II	Beck Depression Inventory
CCHS	Canadian Community Health Survey
CI	confidence interval
CIDI-SF	Composite International Diagnostic Interview Short Form
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3th edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECA	epidemiologic catchment area
HMO	health maintenance organization
HR	hazard ratio
IHS	International Headache Society
MDD	Major Depressive Disorder
MDE	major depressive episodes
NIMH-DIS	National Institute of Mental Health Diagnostic Interview Schedule
NPHS	National Population Health Survey
OR	odds ratio
RDC	Research Data Centre
US	United States
WHO	World Health Organization

Chapter One: Introduction

1.1 Overview of the research problem

Migraine affects people of all ages, genders, and socioeconomic status and can have a major impact on productivity and lifestyle. The impact on people with migraine is reflected in days away from work, hindrance of job performance, restriction of activities and disruption of relationships (Edmeads et al. 1993; Gilmour & Wilkins 2001; Hu et al. 1999; Kryst & Scherl 1994; Sakai & Igarashi 1997; Stang et al. 1998; Stewart et al. 1996; To & Wu 1995). Similarly, major depressive disorder is one of the leading causes of disability worldwide (Ustun & Kessler 2002); the World Health Organization estimates that depressive disorders will be become the second leading cause of disease burden worldwide by the year 2020 (Simon 2003). An association between major depressive episodes (MDE) and migraine has been observed in both population-based studies and in clinical settings (Afifi et al.. 2005; Breslau & Davis 1992; 1993; Breslau et al. 1994a; Breslau et al. 2003; Breslau et al. 1994b; Haarasilta et al. 2005; Jelinski et al. 2007; Jette et al. 2008; Lanteri-Minet et al. 2005; Magnusson & Becker 2003; Merikangas et al. 1990; Merikangas et al. 1993a; Merikangas et al. 1994; Patten et al. 2008; Swartz et al. 2000; Zwart et al. 2003). Major depressive episodes in those with migraine may exacerbate the impact of the condition and complicate treatment (Lipton et al. 2001a) resulting in greater health resource use in migraineurs compared to non-migraineurs (Jette et al. 2008).

1.2 Key definitions

Migraine (Waldman 2009) is defined as a periodic unilateral headache characterized by significant pain that may last hours or days. Migraines are often accompanied by nausea, vomiting, and extreme sensitivity to light (photophobia) and sound (sonophobia), as well as alterations in appetite, mood, and libido. Migraine may or may not be associated with an aura. Migraines with aura are preceded by a physical warning usually occurring 30 to 60 minutes prior to the headache pain although can occur by themselves without the headache pain. Migraine auras are most commonly visual, consisting of blind spots or shimmering lights in the field of vision, called scintillating scotomas. Other aura types include, but are not limited to, motor weakness, language abnormalities or tingling of the face, or extremities. The gold standard for the diagnosis of migraine are the diagnostic criteria from the International Headache Society (IHS): 1) at least five attacks; 2) headache attacks lasting at least four hours; 3) at least two of the following: (a) unilateral pain, (b) pulsation, (c) inhibition of daily activities, (d) aggravation by routine physical activity; and 4) either (a) nausea or vomiting or (b) photophobia and phonophobia (Appendix A).

Major depressive episode is the cluster of symptoms characteristic of major depressive disorder, in which recurrent MDE typically occurs, and is characterized by severe highly persistent major depression, and/or a loss of interest or pleasure in everyday activities, and which is often manifested in a lack of appetite, chronic fatigue, and sleep disturbances. The gold standard for diagnosing MDE is based on the formal Diagnostic and

Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria. Over a two week period, the individual must have consistently experienced five or more symptoms (Appendix C) and these must be outside the parameters of the individual's normal functioning. These symptoms must not fulfil the criteria for mixed episodes (dysphoric mania or agitated depression), nor be due to direct physiological effects of a substance or a general medical condition, nor be better accounted for by the loss of a loved one.

1.3 Study purpose

Using population-based data from Canada, the purpose of this study is to assess the association between MDE and incident migraine and the association between migraine and incident MDE.

1.4 Significance of the study

This study will be the first to provide a comprehensive analysis based on 12 years of prospective follow-up data to examine the association between MDE and migraine. Three possible outcomes for this study include an effect of migraine on MDE risk, an effect of MDE on migraine risk, or both. The significance of this study is partially that the distinctions that can be drawn between these three possibilities have significance for causality, but also because the data support an anticipation of risk. This type of data is important for monitoring patients in different clinical settings as well as for service

planning because it is possible that special arrangements for assessment and/or treatment of one problem may be beneficial in settings where the other is managed.

1.5 Study objectives

The objectives of the current study are to (1) determine the cross-sectional association between migraine and MDE at each of the seven available cycles of the NPHS; (2) determine the 12 year cumulative incidence of migraine in a cohort of participants with MDE at baseline; (3) determine the 12 year cumulative incidence of MDE in a cohort of participants with migraine at baseline; (4) determine the age and sex adjusted 12 year cumulative incidence of migraine in a cohort of participants with and without MDE at baseline (using stratified analysis); (5) determine the age and sex adjusted cumulative incidence of MDE in a cohort of participants with and without migraine at baseline (using stratified analysis); and (6) determine if the observed associations between migraine and MDE, or lack thereof, persist following adjustment for a variety of potential confounding, interacting, or intermediary variables using multivariable modelling.

A literature review on the cross-sectional and longitudinal association between migraine and MDE is given in Chapter 2. Chapter 3 reviews the study methods. The study results are presented in Chapter 4. Chapter 5 discusses the key findings, potential impact of bias, potential role of chance, findings in relation to other studies, strengths, and limitations of the study, and areas for future research.

Chapter Two: Literature review

The purpose of the following literature review is to provide a detailed summary of cross-sectional and longitudinal studies examining the association between MDE and migraine. The emphasis of this review will be on Canadian studies, however as there are a limited number of Canadian studies, non-Canadian studies will also be included. The first two sections will summarize the epidemiology of MDE and the epidemiology of migraine. The third section will summarize cross-sectional population-based studies about the association between MDE and migraine. The final section will summarize findings from population-based longitudinal studies, including some that specifically addressed the possibility of a relationship between MDE and migraine risk and between migraine and MDE risk.

2.1 Descriptive epidemiology of major depressive episodes (MDE)

2.1.1 Prevalence of MDE

In Canada, the data from the population health surveys (Canadian Community Health Survey (CCHS) and the National Population Health Survey (NPHS)), show that the estimated 12 month prevalence of MDE ranges from 4.1% to 6.5% (Beaudet 1999; Patten et al. 2006). Similarly, in the United States (US), the annual prevalence of MDE is estimated at 6.6% (Kessler et al. 2003). The 12 month prevalence of MDE among women (5.7% to 7.1%) in Canada is approximately twice that of men (2.7% to 3.3%) (Beaudet

1999; Patten et al. 2006). The annual prevalence of MDE peaks between the ages of 15 to 24, declines in mid-life, and is lowest among those aged 65 or older (Patten et al. 2006). The prevalence of MDE amongst adolescents aged 12 to 19 in Canada is estimated to be 6.5%, 9.8% in women and 3.4% in men (Afifi et al. 2005). The lifetime prevalence of MDE in Canada has been estimated at 12.2% (Patten et al. 2006) and in the US is estimated to be 16.2% (Kessler et al. 2003).

2.1.2 Incidence of MDE

In Canada, one, two, and three year cumulative incidence proportions of MDE estimated from the NPHS were 2.9%, 5.7%, and 7.2% respectively (Wang et al. 2009). Data from the 1996/1997 and 1998/1999 cycles of the NPHS estimated the two year cumulative incidence of MDE to be 5.7% and the three year cumulative incidence to be 7.7% (Wang et al. 2009). These estimates are consistent with the 3.5 year cumulative incidence of MDE (6.5%) (Breslau et al. 1994a) reported by a population-based study from the US. In the US, the estimated incidence of MDE per 1,000 person years is also higher in women than men, estimated to be 24.0/1,000 (CI 17.4-31.9) for women and 10.2/1,000 (CI 5.3-17.9) for men (Breslau et al. 1994a).

2.1.3 Risk factors for MDE

2.1.3.1 Sex and age

In Canada, women are at higher risk of developing MDE (Patten 2000; Patten et al. 2006; Wang et al. 2009) while the incidence of MDE decreases with increasing age (Wang et al. 2009). Women have also been reported to be at higher risk of developing major depression in the US (Breslau et al. 1994a).

2.1.3.2 Health conditions and other factors associated with MDE

The literature about the epidemiology of MDE in Canada shows that smoking and certain environmental factors, including chronic strain and recent negative events, increase the odds of having MDE (Patten et al. 2006). Specific chronic health conditions also increase the risk of incident MDE (Wang et al. 2009) as do certain social and psychological factors such as previous major depressive episodes, and among women, lack of social support and lower sense of mastery (Patten et al. 2006). Among women, traumatic events in childhood or young adulthood increase the risk of MDE (Patten et al. 2006). A family history (sibling or parent) of depression has been found to be one of the strongest predictors of MDE in Canada (Wang et al. 2009). In the NPHS, respondents with a family history of depression were approximately twice (Beaudet 1996; Wang et al. 2009) as likely to develop MDE compared to persons who had no close family members with a history of depression.

2.2 Descriptive epidemiology of migraine

2.2.1 Prevalence of migraine

In Canada, the lifetime prevalence of migraine is estimated to be around 7% to 17% (Edmeads et al. 1993; Gordon et al. 2004; Jelinski et al. 2006; O'Brien et al. 1994; Pryse-Phillips et al. 1992), while the population-based annual prevalence is between 8% to 9.4% (Gilmour & Wilkins 2001; Jette et al. 2008; Molgat & Patten 2005). Canadian studies found that approximately 50% of individuals classified as having migraine according to the IHS criteria had never been diagnosed with migraine by a physician (Cooke & Becker 2010; O'Brien et al. 1994). Canadian estimates relying on national health survey data may under-ascertain the prevalence of migraine as they rely on self-report of migraine diagnosed by a health professional. Despite the possible underestimation of the prevalence of migraine in Canada, Canadian estimates are still in keeping with those from US population-based studies (American Migraine Survey) that use the IHS criteria (Breslau & Rasmussen 2001; Lipton & Bigal 2005; Lipton et al. 2002; Lipton & Stewart 1994).

The prevalence of migraine in Canada is estimated to be three times as common in women at 11.9% to 15.2%, compared to men at 3.8% to 6.1% (Gilmour & Wilkins 2001; Jette et al. 2008). The higher prevalence of migraine among women has also been documented in non-Canadian population-based studies in the US (Bigal et al. 2004; Lipton

1998; Lipton et al. 2001a) and in Europe (Henry et al. 1992; Rasmussen 1993; 1995a; b; Steiner et al. 2003).

The peak prevalence of migraine in Canadians is estimated to occur during midlife between 25 and 44 years, (Jette et al. 2008) and is consistent with estimates from the US (Lipton et al. 2001a; Lipton et al. 2002; Lipton et al. 2001b). The literature shows that the prevalence of migraine increases throughout childhood and early adulthood until the age of 40 years at which time it declines (Bigal et al. 2004). In the US, the onset of migraine was reported to begin at a later age in women compared to men (Stewart et al. 1991). Peak incidence of migraine with aura was estimated at 13 to 14 years in women and 5 to 6 yrs in men (Stewart et al. 1991). Peak incidence of migraine without aura was estimated at 14 to 16 years in women and 10 to 11 years in men (Stewart et al. 1991).

2.2.2 Incidence of migraine

A limited number of population-based longitudinal studies have investigated the incidence of migraine. The annual incidence of migraine ranges between 2.1 to 4.8 per 100 individuals according to cycles 1994/1995 to 2002/2003 of the NPHS (Patten et al. 2008), while data from the 1994/1995 to 1998/1999 cycles of the NPHS estimated the four year cumulative incidence of migraine to be 3.8 cases per 100 individuals (Gilmour & Wilkins 2001). Similarly, data from the US has estimated the 3.5 year cumulative incidence of migraine to be 5.3 (CI 3.8-6.8) per 100 individuals (Breslau et al. 1994b).

Statistical modeling techniques based on the age of onset of migraine have been used to estimate the cumulative incidence of migraine from population-based cross-sectional data in the US. Using these methods, the cumulative incidence of migraine (by the age of 85) has been estimated to be 18.5% in men and 44.3% in women (Stewart et al. 2008). These estimates are higher than the lifetime prevalence cited above. Lifetime prevalence estimates include respondents that have not yet been exposed to the entire risk interval and are therefore expected to be lower than projected cumulative incidence.

2.2.3 Risk factors for migraine

2.2.3.1 Sex and age

Four year cumulative incidence data from early cycles of the NPHS show that women (5.7 per 100) are at greater risk for migraine compared to men (1.9 per 100) (Gilmour & Wilkins 2001) in Canada. This is consistent with US population-based data showing that the incidence per 1,000 person years in women (22/1,000) was up to four times that of men (5/1,000) (Breslau et al. 1994a).

2.2.3.2 Mental health conditions and other factors associated with migraine

Population-based studies from both Canada and the US show that migraine prevalence is inversely related to household income (Jette et al. 2008; Lipton 1998; Lipton et al. 2001c). The literature also suggests that poor diet, poor medical care or stress

associated with low income may contribute to the higher prevalence of migraine (Scher et al. 2005). In Canada (Jette et al. 2008), mental health conditions associated with migraine include major depressive disorder, bipolar disorder, panic disorder, and social phobia.

2.3 Population-based studies on the association between MDE and migraine

Two national population health surveys, the CCHS and NPHS, provide epidemiological data representative of the general population in Canada. The following literature review of the association between MDE and migraine will focus on data from the CCHS and the NPHS, and a few international studies that have used standardized diagnostic criteria to measure migraine and MDE are also included.

Research about biological mechanisms of the MDE-migraine connection has often focused on the common neurobiology (Frediani & Villani 2007), serotonergic function and glutaminergic transmitter systems (Muller & Schwarz 2007; Pietrobon 2005; Schur et al. 2009; Stam et al. 2010) of the brain, and shared genetically determined disease mechanisms (Stam et al. 2010). These particular studies will not be reviewed here.

2.3.1 Cross-sectional association between MDE and migraine

Jette (Jette et al. 2008) measured the co-occurrence of migraine and psychiatric disorders using data from the 2002 CCHS 1.2 on Mental Health and Wellbeing, which was a nationally representative household survey of adults 15 years of age and older

(n=36,984). This health survey included administration of the World Mental Health Composite International Diagnostic Interview (WMH-CIDI) to produce a diagnosis of major depressive disorder (MDD) according to the DSM-IV criteria. Migraine diagnosis was based on self-report of migraine that was diagnosed by a health professional. In this population, the 12 month prevalence of MDD in migraineurs (8.6%, CI 7.3-9.8) was over two times (adjusted OR 2.3, CI 1.9-2.8) that of non-migraineurs (3.4%, CI 3.1-3.7). Similarly, the lifetime prevalence of MDD in migraineurs (18.8%, CI 17.0-20.5) was double that of non-migraineurs (9.8%, CI 9.3-10.3). The association between MDD and migraine did not differ between men and women, however women had a higher, although not significant, prevalence of migraine and MDD than men. The 12 month prevalence of MDD in migraineurs who were widowed, separated, divorced or in the lowest and lower middle income categories was higher than that of their non-migraineurs counterparts.

Afifi (Afifi et al. 2005) investigated health determinants associated with adolescent MDE in Canada. Data about adolescents (aged 12 to 19) from the 2000 CCHS 1.1 were included in the study (n=17,557). MDE was assessed by the number of depressive symptoms expressed by each respondent based on the DSM-IV criteria as applied by the Composite International Diagnostic Interview Short Form (CIDI-SF). The magnitude of the association between MDE and migraine obtained from logistic regression were similar for adolescent men (OR 1.5, CI 1.4-1.5) and adolescent women (OR 1.3, CI 1.2-1.3).

Molgat (Molgat & Patten 2005) also used data from the CCHS 1.1 to estimate the prevalence of MDE in respondents with migraine and compared the strength of the association with that of other long term medical conditions. Migraineurs had more than a twofold (OR 2.6, CI 2.4-2.8) increase in the prevalence of MDE, a stronger association than that seen in most other medical conditions.

Non-Canadian population-based cross-sectional studies assessing the association between MDE and migraine have found the prevalence of MDE to be elevated in individuals with migraine using both unadjusted and prevalence ratios adjusted by sex, age education (Lipton et al. 2000; Lipton et al. 2002; McWilliams et al. 2004; Patel et al. 2004; Rasmussen 1993; 1995b; 1999; Rasmussen & Olesen 1993; 1994; Zwart et al. 2003).

Finally, clinical studies have used different measurement tools than epidemiological studies to measure outcomes. Recent clinical studies (Jelinski et al. 2007; Magnusson & Becker 2003) in Canada have examined the association between migraine and symptoms of MDD in patients referred to headache specialists in Canada. In these studies, symptoms of MDD were assessed with the Beck Depression Inventory (BDI-II), a 21 item scale measuring the severity of key symptoms associated with clinical MDD. The diagnosis of migraine with or without aura was made using the IHS criteria. Similar to epidemiological studies, results (Jelinski et al. 2007; Magnusson & Becker 2003) from these recent clinical studies consistently show an association between MDD and migraine, especially migraine with aura.

2.3.2 Longitudinal association between MDE and migraine

Population-based longitudinal studies estimating the risk of incident migraine in those with MDE and the risk of incident MDE in those with migraine are sparse (Breslau & Davis 1993; Breslau et al. 1994a; Breslau et al. 2003; Merikangas et al. 1993b; Patten et al. 2008; Swartz et al. 2000). However, the literature remains mixed and weak as to whether MDE increases the risk of migraine. This review of the longitudinal population-based studies examining the association between MDE and migraine will include a summary of the: 1) risk of MDE with migraine, 2) risk of migraine with MDE, and 3) studies assessing the bidirectional association between the two conditions.

2.3.2.1 Risk of incident MDE with prior migraine

In a longitudinal population-based study, Patten (Patten 2001) measured the incidence of MDE among persons 15 years or older (n=11,859), with and without long term medical conditions using data from the first (1994/1995) and second cycles (1996/1997) of the NPHS. Migraine was one of three long-term medical conditions most strongly associated with incident MDE.

A retrospective cohort study by Breslau (Breslau & Davis 1993) of a random sample (n=1,007) of young adults (21-30 years) drawn from a large health maintenance organization (HMO) in southeastern Michigan was interviewed in 1989 and in a follow-up interview 14 months later. The study examined whether persons with a history of migraine,

collected at baseline, were at an increased risk of developing incident MDD. MDD was assessed by the National Institute of Mental Health Diagnostic Interview Schedule (NIMH-DIS) based on the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R). Assessment of migraine was based on a sequence of questions adapted from the IHS criteria. The study showed that prior migraine conferred an approximately fourfold increase (odds ratio (OR): 4.2, confidence interval (CI): 2.0-9.2) in the risk of incident MDD. The wide confidence interval for the reported odds ratios in this study indicates lack of precision of the estimates due the small size of the study sample.

2.3.2.2 Risk of incident migraine with prior MDE

A longitudinal study of respondents (12 years or older) (n=14,084) by Patten (Patten et al. 2008) based on data from the first five cycles of the NPHS (1994/1995 to 2002/2003) assessed the incidence of chronic medical conditions in people with and without MDE in Canada. The proportional hazard models to assess incident migraine used two different variations in the measurement of the exposure (MDE). First, MDE at the baseline interview (1994/1995) was used to define and separate the depressed from the non-depressed respondents at risk for MDE. Second, MDE was treated as a time-varying factor, so that MDE status at the start of each two year incidence interval determined whether a respondent was in the exposed on non-exposed cohort during that interval. Results from proportional hazards regression modeling showed that unadjusted hazard ratios for incident

migraine were elevated using both baseline and time-varying measures of MDE. An interaction between age and presence of MDE suggested that the association between migraine and MDE was present only in respondents under the age of 26 years. The analysis was therefore restricted to respondents under the age of 26 years. The two unadjusted hazard ratios obtained from baseline measurement of MDE (HR 1.9,CI 1.0-3.8) and time-varying measurement of MDE (HR 2.8,CI 1.6-5.0) showed the association between MDE and incident migraine moved in the same direction however the magnitude of the association was stronger in time-varying analyses. In the time-varying (MDE) analyses, the hazard ratio for incident migraine diminished after adjustment for age, sex, and health care use (adjusted HR 2.1, CI 1.2-3.6), but an association remained evident. The authors concluded that the strength of the association between MDE and incident migraine depended on age and was evident only in respondents under 26 years.

In the Baltimore cohort of the Epidemiological Catchment Area (ECA) study, Swartz (Swartz et al. 2000) investigated the association between affective disorders and the incidence of migraine in a prospective cohort study. The at risk population (n=1343) for the study of incident migraine included only adults who had given negative responses to a series of questions about headache, although not migraine specifically, in the baseline interview (1981). A prospective follow-up interview conducted approximately 14 years later was based on the IHS criteria for migraine. The measurement instrument for MDE was the NIMH-DIS. The sex and age adjusted odds ratio (0.68, CI 0.24-1.97) was lower

than estimates from Patten (Patten et al. 2008) and Breslau (Breslau et al. 1994a; Breslau et al. 1994b). One of the limitations of this study was the lack of detailed information about headaches from the baseline interview. The authors acknowledged that the exclusion of individuals with a history of unspecified headaches at the baseline interview might have influenced the results leading to a conservative estimate of incident migraine, thus accounting for the lower point estimate than in other studies. Random errors may also account for the lack of association found in this study. The wide confidence intervals around the point estimate indicate lack of precision of the estimate. The study may therefore have been underpowered due to the small sample size.

2.3.2.3 Bidirectional association between migraine and MDE

In a second follow-up (Breslau et al. 1994a) to a prior retrospective cohort study (Breslau & Davis 1993)**,** a cohort of young adults were re-interviewed 3.5 years after the baseline interview (1989) in order to assess the bidirectional association between MDD and migraine. This study combined baseline data on lifetime history of MDD and migraine and follow-up data covering the 3.5 year interval to produce estimates of the conditional risk of first onset MDD as a function of prior history of migraine and the conditional risk for first onset migraine as a function of prior MDD. Cox-proportional hazards models with age of onset of migraine (or MDD) as a covariate were used to estimate the relative risk for MDD (or migraine) associated with prior migraine (or MDD). This study suggested that the

previously observed cross-sectional association between migraine and MDD resulted from bidirectional influences, with each disorder increasing the risk for first onset of the other. Results revealed an approximate threefold increase in the risk of incident migraine with prior MDD (sex adjusted HR 3.3, CI 2.1-5.3) and nearly the same risk of incident MDD with prior migraine (sex adjusted HR 3.4, CI 2.4-4.8). The association of each disorder with the other applied equally to men and women although both disorders were more common in women. This study covered only incident cases occurring in persons aged 22 to 33 years of age and therefore cannot inform on persons with an earlier or later onset of the disorders. The selection of participants drawn from members of a HMO rather than the general community may reduce the generalizability of these results. Although the study followed a cohort prospectively for over three years, the exposure (to either migraine or MDD depending on the outcome) occurred prior to the start of the study. Recall bias, a form of information bias, may have been introduced due to memory errors about the history of the onset of either migraine or MDD. If present, this information bias would likely create non-differential misclassification pulling the measure of association towards the null; therefore, the magnitude of the association may be larger than it appeared in the study results.

A retrospective cohort study (migraine vs. control) by Breslau (Breslau et al. 2003) based on data from the Detroit Area Study of Headache investigated factors contributing to the bidirectional association between MDD and migraine. In this study, adult participants selected from a prior retrospective cohort study (2000) were re-interviewed. At the start of

the initial study (Breslau et al. 2000), subjects were selected for the three study groups (migraine, n=496; severe headache, n=151; and control, n=539) based on interview questions about medical history. In the subsequent follow-up study, the 1,186 adults were re-interviewed two years later (2003). Controls were excluded if they met criteria for either migraine or severe headache, or reported a history of nausea, vomiting, photophobia or phonophobia associated with a headache or had ever experienced headaches with a pain severity score greater than mild. Differences in the participation rate between the migraine and control groups were small. Control subjects were matched to the migraine subset, on sex, age (within five years), and race. The authors intentionally restricted the sample to persons in the age range (25 to 55) of peak migraine prevalence in order to maximize the statistical power of the study. The two year incidence of migraine was 9.3% in control subjects with prior MDD versus 2.9% in control subjects without prior MDD. The magnitude of the association (unadjusted OR 3.4, CI 1.4-8.7) between prior MDD and incident migraine among the at risk members of the control group diminished slightly after adjustment for sex and comorbid psychiatric disorders (OR 3.0, CI 1.2-7.6). Incident MDD was compared across the migraine and control subjects. The two year incidence of MDD in those with migraine was 10.5% compared to 2.0 % in the control group. The unadjusted OR for incident MDD in persons with migraine (with controls as a reference) was 5.8 (CI 2.7-12.3) and the OR adjusted for sex and comorbid psychiatric disorders was 5.2 (CI 2.4-11.3). These estimates indicate a stronger association than that observed in similar studies.

Sex and comorbid psychiatric adjusted odds ratios were presented, however no adjustments for age were reported, therefore, effect modification and/or confounding by age is possible. The authors did attempt to control for confounding by matching the migraine and control group by age (within five years). However, not adjusting for age in the multivariate logistic regression models may have left some residual confounding. Likewise, effect modification may have occurred if the MDD-migraine association was heterogeneous across different age strata. By not accounting for age, the presented estimates can be viewed as weighted averages across the different age strata. The confidence intervals for the odds ratios are considerable and this may be due to large differences in the stratum specific age estimates. The impact of any effect modification or residual confounding by age is unlikely to account entirely for the strong bidirectional association. If the true associations were weakened by the adjustment for age, the estimates would be closer to those reported in other studies. In addition, the wide confidence intervals for the reported odds ratios in this study indicate lack of precision of the estimates due the small size of the study sample. The authors did not adjust for childhood traumas or life stress.

In a 1993 retrospective study**,** Merikangas presented results from a 10 year follow-up (Merikangas et al. 1993b) of a birth cohort of 379 young adults selected from the general population of Zurich, Switzerland. This study investigated the association between migraine, anxiety, and MDE in this young birth cohort aged 17 to 18 years old. Psychiatric diagnoses were made according to both the DSM-III and DSM-III-R criteria. The baseline

(1979) diagnostic criteria for migraine developed by a neurologist was modified at follow-up (1988) to incorporate IHS criteria. This study reported on the chronology of migraine and MDE in persons with the two disorders. This study suggested that the onset of MDE generally follows the onset of migraine by an average of three years. In this study the diagnostic instrument used to assess major depression for the birth cohort in 1979 was the Structured Diagnostic Interview for Psychopathologic and Somatic Syndromes (SPIKE), a semi structured instrument that was developed for epidemiological studies that has not been widely used (Radat & Swendsen 2005). Limited details about the statistical analysis regarding the assessment of both incident migraine and incident MDE make it difficult to ascertain if the results were affected by bias, effect modification or confounding.

2.3.3 Summary of the literature about the association between MDE and migraine

Population-based cross-sectional studies have consistently reported an association between migraine and MDE (Breslau et al. 2000; Haarasilta et al. 2005; Jette et al. 2008; Kececi et al. 2003; Lanteri-Minet et al. 2005; Lipton et al. 2000; Merikangas et al. 1990; Patten 2001; Zwart et al. 2003). However, population-based longitudinal studies are often inconsistent in their methodological approaches and reporting of the association. First, although few in number, longitudinal studies consistently report an association between migraine and incident MDE. These studies generally show that migraine elevates the risk of MDE (Breslau & Davis 1993; Patten et al. 2008) between four to six times. Second, the

literature about the longitudinal association between MDE and incident migraine is limited and the few studies on the topic show inconsistent findings. Patten (Patten et al. 2008) and Breslau (Breslau et al. 1994a; Breslau et al. 2003) found that MDE increases the risk of incident migraine between two to six times. However, Swartz (Swartz et al. 2000) found no association between MDE and incident migraine in the Baltimore ECA study. Third, the very limited epidemiological studies of the bidirectional association between MDE and migraine used varying methodology and reported conflicting results. The two studies from Michigan (Breslau et al. 1994a; Breslau et al. 2003) relied on samples selected from members of a HMO rather than the general population making their results less generalizable than population-based epidemiological studies. Finally, the Zurich (Merikangas et al. 1990; Merikangas et al. 1993a) study examining the longitudinal association between MDE and migraine was afflicted with questionable methodology making the results difficult to interpret. The inconsistency between the results of these longitudinal studies on the bidirectional association between migraine and MDE may be due to several factors including: differences in populations from which sample were drawn, samples' ages, length of recall period, and assessment procedures of persons at risk.

This Canadian population-based study is important as it may better define the bidirectional association between MDE and migraine. This requires an examination of the associations between migraine and incident MDE and MDE and incident migraine. Several reasons make this study a vital addition to the literature on this topic. First, unlike the two

studies from Michigan (Breslau et al. 1994a; Breslau et al. 2003) examining the bidirectional association between migraine and MDE, the current study is based on a very large cohort. Thus, it is less likely to be underpowered and therefore less likely to produce imprecise estimates as did the study by Breslau (Breslau et al. 2003), which reported very large confidence intervals. Second, unlike the Michigan studies (Breslau et al. 1994a; Breslau et al. 2003), the current study is based on the general population. As such, it will be more generalizable than studies from selected samples such as HMO cohorts. Third, this study is inclusive of persons over the age of 12 at the 1994/1995 baseline interview rather than being limited to a cohort of individuals over the age of 17 at the start of the study (Breslau & Davis 1993; Breslau et al. 1994a; Breslau et al. 2003; Merikangas et al. 1990; Merikangas et al. 1993a; Swartz et al. 2000). This may be an important difference in view of the, often young, age of onset of both migraine and MDE. Finally, the length of follow-up, 12 years for the current study, is considerably longer than that of any of the longitudinal studies examining the association between MDE and migraine.

Chapter Three: Methods

3.1 Background of the National Population Health Survey (NPHS)

Statistics Canada, a federal government agency, is responsible for the creation, management, and administration of the NPHS. The NPHS collects both cross-sectional and longitudinal data on the economic, social, demographic, occupational, and environmental correlates of health, making this survey a rich source of epidemiological data about the health status of Canadians. The NPHS has two components: one for household residents and another for residents of institutions. The household component was used in this study, and for ease of language is subsequently referred to as the NPHS. The NPHS is administered to a panel of individuals (cohort) who are followed over time to reflect the dynamic process of health and illness (Swain et al. 1999). The first cycle of data collection took place in 1994/1995 with subsequent cycles every two years thereafter (1996/1997, 1998/1999, etc.). To date, seven cycles of the longitudinal data are available for analysis and are the source of data for the current study. The general component of the NPHS questionnaire contains demographic, socioeconomic, and limited health information about all members of a selected household, while information from the health component contains detailed health questions and is administered to only one randomly selected individual per household (Swain et al. 1999). The health component was used in this study.

3.2 Target population of the NPHS

The target population of NPHS includes household residents in the ten Canadian provinces, comprising 98% of the national population. Residents of institutions, homeless people, and people living on Indian reserves, Crown Lands, or on Canadian Forces bases were excluded from the sampling frame. Some remote areas of Quebec and Ontario were also excluded.

3.2.1 Sampling

3.2.1.1 Sample design of the NPHS

The NPHS employed a stratified multi-stage study design (clusters, dwellings) that used Statistics Canada's Labour Force Survey sampling frame, except in the province of Québec where Santé Québec's "Enquête sociale et de santé" was used (Swain et al. 1999). In general, clusters were created by consideration of province, major urban centers, towns (urban or rural), and then geographic and or socioeconomic strata (Swain et al. 1999). Dwellings were chosen from within these clusters. In 1994/1995, the initial sample was created by first selecting households and then within each household, choosing one member 12 years of age or older to be the longitudinal respondent (Statistics Canada 2010).

3.3 Data collection of the NPHS

Data collection for the NPHS took place in each of the four seasons and was performed through computer-assisted interviewing (CAI) procedures (Swain et al. 1999). The initial 1994/1995 NPHS panel interviews were conducted primarily through personal interviews at the selected dwellings, while approximately 98% of subsequent re-interviews were conducted by telephone. Various strategies were used to improve response rates including: interviewer-training, use of languages other than French and English to conduct interviews, rescheduling interviews when needed, non-response follow-up, and tracing of respondents who moved. Refusals were followed up by senior interviewers specially trained in tracing respondents. In 1994/1995, 20,095 people were selected for the NPHS longitudinal panel, 17,276 agreed to participate, for a response rate of 86.0% (Swain et al. 1999). The response rate for follow-up cycles were: 92.8% (1996/1997), 88.2% (1998/1999), 84.8% (2000/01), 80.6% (2002/2003), 77.6% (2004/2005), and 77.0% (2006/2007)(Statistics Canada 2010). By the seventh cycle in 2006/2007 (the endpoint of the current analysis), 2,032 of the original respondent were deceased, 148 had been institutionalized, and 3,977 were classified as non-respondents due to loss to follow-up because of refusal or failure to trace (Statistics Canada 2010).

3.4 Data management

Longitudinal data from the NPHS are available in several file formats depending on the inclusion of full or partial information. Respondents who were interviewed at each of the seven cycles would have provided full information. Respondents leaving the sampling frame due to death, institutionalization or homelessness would have only contributed partial information in the cycles in which they were interviewed. The NPHS data file used in this study (longitudinal square file) contained seven cycles (1994/1995 to 2006/2007) with both full and partial data for the 17,276 individuals randomly selected (in 1994/1995) to the longitudinal sample irrespective of the their status in subsequent cycles. Data collected by Statistics Canada is made available through Research Data Centers (RDC) across Canada. The RDCs provide researchers in a secure university setting with access to data from population and household surveys including the NPHS. Strict guidelines ensure confidentiality under the requirements of the Statistics Act. Projects must be approved before access is granted and all data analysis must be completed using the computers at the RDCs. A stringent disclosure procedure requires all results to be screened to ensure confidentiality before they are allowed to leave the secure research environment. All analyses for this study were conducted at the Prairie RDC at the University of Calgary and were screened for approval prior to release. While the research and analysis from this study

are based on data from Statistics Canada, the opinions expressed herein do not represent the views of Statistics Canada.

3.5 Study variables

3.5.1 Major depressive episodes

The NPHS interview included the CIDI-SF (Kessler et al. 1998) for MDE, which assesses past year MDE. Trained Statistics Canada interviewers administered the CIDI-SF. These interviewers were not health professionals. However, it should be noted that the CIDI-SF is designed for use by non-health professionals and is fully structured so that clinical judgement is not required, or allowed, while administering the interview. The CIDI-SF is scored with a predictive probability based on the number of symptom-based criteria fulfilled during the same two week period in the past year. This instrument also requires that depressed mood, loss of interest or pleasure in usually enjoyed activities, or both, be reported. The CIDI-SF is based on the DSM-III-R classification for MDE. According to the DSM-III-R, a major depressive episode must include five of the following nine key symptoms lasting at least two weeks and being associated with a change in functioning, and including either depressed mood or loss of interest:

1) Depressed mood
2) A significantly reduced level of interest or pleasure, in all or nearly all usually-enjoyed activities.
3) A considerable loss or gain of weight or a subjective change in appetite.

4) Difficulty falling or staying asleep (insomnia) or sleeping more than usual (hypersomnia).
5) Psychomotor agitation or retardation.
6) Feeling fatigued, or diminished energy.
7) Thoughts of worthlessness or extreme guilt (not about being ill).
8) Ability to think, concentrate, or make decisions is reduced.
9) Frequent thoughts of death or suicide, or attempted suicide.

In the NPHS, MDE status is indicated by a derived variable that calculates the predicted probability that a respondent would have been diagnosed with a major depressive episode in the past 12 months if they had completed the (long-form) CIDI. The predicted probability was assigned based on respondents' short-form scores based on symptoms reported during the same two week period during the preceding year (Statistics Canada 2009a). For this project, if the estimated predicted probability was 0.9 or more, the respondent was considered to have experienced a MDE in the previous 12 months. Not surprisingly, the 90% predictive cut-point coincides with a respondent's reporting of five of the nine specified symptom-based criteria. The specific questions in the MDE module of the NPHS questionnaire are included in Appendix B.

3.5.2 Migraine

The NPHS subjects were read a list of chronic medical conditions and asked whether they had been diagnosed with one of these conditions by a health professional. The

actual wording of the item was “Now, I would like to ask about certain chronic health conditions that you may have. We are interested in long-term conditions that have lasted, or are expected to last, six months or more and that have been diagnosed by a health professional.” This was followed by a series of specific questions including: “Remember, we’re interested in conditions diagnosed by a health professional. Do you have migraine headaches?” Respondents answering *yes* to this question were identified as having migraine.

3.6 Other variable definitions

The following set of demographic, socioeconomic, psychosocial, and health related variables were included in the analyses because they were judged potential effect-modifying or confounding variables based on existing literature (see Chapter 2). In two separate stages of analysis, both MDE and migraine acted as exposure and outcome variables. Variables thought likely to be associated with either MDE or migraine were regarded as potential confounding variables and are listed below.

3.6.1 Demographic variables

The NPHS measured a number of demographic variables. Sex, age, and marital status were deemed possible confounders, or effect modifiers, in these analyses. In the NPHS, sex was classified at the initial face-to-face interview.

Age at baseline (1994/1995) was treated as a categorical variable and was collapsed into three categories for analysis: 12 to 25, 26 to 45, 46 years and older. The decision to use these age categories was made during the course of the analysis in order to ensure an adequate number of endpoints within strata. In addition, previous projects using the NPHS MDE data found that these categories provided an adequate number of endpoints in their analyses (Bulloch et al. 2009; Wang et al. 2009).

In the NPHS data file, the seven marital-status categories were: married, living common-law, widowed, separated, divorced, single, and never married. For the purpose of this study, marital status was collapsed into three categories: 1) single, 2) formerly married (widowed/separated/ divorced), and 3) married (married/common-law). Similar to previous studies using the NPHS dataset, the small number of widowed, separated, and divorced respondents were combined into a formerly married category in order to ensure adequate numbers of endpoints for analysis within strata.

3.6.2 Socioeconomic status variables

The NPHS measured a number of socioeconomic status variables. Household income and education were deemed possible confounders in this analysis. The variables are described here.

3.6.2.1 Household income

The household income variable corresponds to the NPHS income adequacy item. which is a dichotomous measure based on "Low Income Cut-offs" (LICO). LICO's convey the income level at which a family may be in strained circumstances because it had to spend a greater proportion (20% or more) of its income on necessities (food, shelter, and clothing) than the average Canadian family of similar size (Statistics Canada 2009a). This variable is based on self-reported income from all sources in the previous 12 months adjusted for the number of people living in the household. Household income was grouped into two categories (low family income vs. middle or high family income) using the categories listed in Table 2.1

Table 2.1 Household income categories

	Income	Household size
Low family income	Less than $15,000	1 or 2 persons
	Less than $20,000	3 or 4 persons
	Less than $30,000	5 or more persons
Middle or high family income	$15,000 or more	1 or 2 persons
	$20,000 or more	3 or 4 persons
	$30,000 or more	5 or more persons

3.6.2.2 Educational attainment

This item classified respondents based on highest level of education attained categorized at two levels: secondary education or less versus at least some post-secondary education. This approach to categorization of the variable was based on the literature of epidemiological studies of MDE in Canada. Prior population-based studies about MDE in Canada have used the same measurement convention for educational status (Patten et al. 2006; Patten et al. 2009; Wang et al. 2009). One (Patten et al. 2009) of these studies explained the rationale for adopting this measurement indicating that people with the lower level of education according to this categorization are a socioeconomically distinct group.

3.6.3 Psychosocial variables

The NPHS asked a number of questions about psychological and social resources. In 1996, Beaudet (Beaudet 1996) used the first cycle (1994/1995) of NPHS data to examine these psychosocial variables as risk factors for MDE. In that study, categorical variables were created by scaling respondents' scores on the multi-item scales designed to measure each of these variables. Tests for internal consistency are only available for some of these scaled psychosocial variables, however the measures possess face validity, have been used by prior studies, and have been field tested by Statistics Canada(Statistics Canada 2009a).

3.6.3.1 Self-esteem

Self-esteem was defined from the following six items in the NPHS. The items were scored using a 5-point scale (0="strongly disagree" to 4="strongly agree") to rate their replies to six statements:

1. You feel that you have a number of good qualities
2. You feel that you're a good person of worth at least equal to others
3. You are able to do things at least as well as most other people
4. You take a positive attitude toward yourself.
5. On the whole, you are satisfied with yourself
6. All in all, you're inclined to feel you're a failure (reverse scale on this item)

Ratings on the six individual items were summed to obtain a total score. Respondents with a total score less than 18 were deemed to have low or very low self-esteem. This cut point for low self-esteem was previously used by Beaudet (Beaudet 1996) in 1996. These questions were only asked in two cycles (1994/1995 and 2000/2001). According to Statistics Canada (Statistics Canada 2009a), documentation of this measure of self-esteem is based on a subset of six items from the Rosenberg's original 10 item scale (Rosenberg 1979).

3.6.3.2 Social support

Social support is based on four dimensions of perceived social support. Respondents were prompted to answer *yes* or *no* to four questions reflecting whether they

feel that they: have someone they can confide in, someone they can count on, someone who can give them advice, and someone who can make them feel loved. Respondents who answered no to one or more questions were considered lacking in at least one meaningful dimension of social support. The measurement tool created by Statistics Canada has not yet been validated, however, this NPHS measure for social support has been used in previous studies on MDE (Beaudet 1996).

3.6.3.3 Stress

The stress variable employed in this analysis was a measure of respondents' general chronic stress. This summative measure was based on 11 true or false statements about stressors including: activity overload, financial difficulties, and problems with relationships in day-to-day encounters. The higher the score, the greater the level of stress. The scores were divided into quartiles; respondents classified in the upper quartile deemed to have a significant level of stress. The measurement tool created by Statistics Canada has not yet been validated but it is a widely used measure of stress in published literature about the NPHS.

3.6.3.4 Childhood trauma

The Childhood trauma variable used in this study was an indicator for traumatic events respondents may have been exposed to during their childhood or young adulthood.

Events included parental divorce, a lengthy hospital stay, prolonged parental unemployment, frequent parental alcohol, or drug use. The precise wording of the childhood trauma item was: "The next few questions ask about some things that may have happened to you while you were a child or a teenager, before you moved out of the house. Please tell me if any of these things have happened":

a) Did you spend two weeks or more in the hospital?
b) Did your parents get a divorce?
c) Did your father or mother not have a job for a long time when they wanted to be working?
d) Did something happen that scared you so much you thought about it for years after?
e) Were you sent away from home because you did something wrong?
f) Did either of your parents drink or use drugs so often that is caused problems for the family?
g) Were you ever physically abused by someone close to you?"

Respondents with one or more *yes* replies were considered to have experienced a childhood trauma. Higher scores indicated more childhood stressors. Statistics Canada produced this index but "analyses of McDowell, Boulet and Kristjansson guided the selection of the items which were part of a pool used in studies conducted by Blair Wheaton" (Statistics Canada 2009a). In this study, childhood trauma is a dichotomized variable (no childhood trauma/some childhood trauma). The NPHS asked this question to anyone 18 years or older.

3.6.4 Health related variables

Chronic health conditions, family history of depression, and smoking status were deemed possible confounders or effect modifiers in this study and therefore described here.

3.6.4.1 Chronic health conditions

If respondents indicated they had any of the 18 listed health conditions, diagnosed by a health professional, and which expected to last ≥ six months, they were deemed to have a chronic health condition. In this study, chronic health condition is a dichotomized variable (yes/no).

Table 2.2 Health conditions included in the chronic condition variable

Allergies other than food allergies	Epilepsy
Alzheimer's disease or dementia	Food allergies
Arthritis/rheumatism (excluding fibromyalgia)	Glaucoma
Asthma	Heart disease
Back problems (excluding fibromyalgia & arthritis)	High blood pressure
Cancer	Sinusitis (cycles 1 to 3 only)
Cataracts	Stomach ulcers
Chronic bronchitis or emphysema	Thyroid condition
Diabetes	Urinary incontinence
Effects of stroke	

Information about each of these chronic health conditions was collected in all seven cycles except for sinusitis, which was only included in cycles one to three.

3.6.4.2 Family history of depression

In cycle six (2004/2005), respondents were asked if any of their close relatives (birth mother, birth father, birth brother, or birth sister) had been diagnosed with major depression by a health professional. For this project, an affirmative response to this question was used as an indicator for family history of depression.

3.6.4.3 Smoking status

Current smoking appears to be a risk factor for MDE (Beaudet 1999; Breslau et al. 1998). Respondents were asked about current and former smoking habits in each NPHS interview. Smoking may also be associated with migraine (Hershey & Lipton 2010) hence potential for it to confound the association between migraine and depression. In order to adjust for the potential of smoking as confounder, two categories of smoking were created: current smoker (current occasional and current daily) and current non-smoker (former daily, former occasional and never).

3.7 Study design

This study design was that of a retrospective cohort. A retrospective cohort study is a form of longitudinal study in which subjects who do not have a disease (or other outcome) are followed over a defined period of time in order to capture the probability of developing new cases of a given disease (or outcome) and in which the composition of the cohort and assessment of the exposure is based on existing (retrospective) data (Porta &

International Epidemiological Association 2008). This study is classified as a retrospective cohort study because it assesses the incidence of either MDE or migraine (depending on the outcome) occurring during the 12 year period between among a cohort who were identified in exposure categories based on their baseline (1994/1995) interview.

To achieve the objectives of this study, two retrospective analyses were conducted. Data from the 1994/1995 NPHS were used as baseline information to select and classify the subjects for each analysis. In the assessment of the outcome of incident MDE, subjects who did not have MDE at the baseline interview were sorted into exposed and non-exposed cohorts based on migraine status at the baseline interview. The exposed (migraineur) and non-exposed (non-migraineur) cohorts were followed for 12 years in order to compare the incidence of MDE. In the assessment of incident migraine, subjects who did not have the outcome of migraine at the baseline interview were sorted into exposed and non-exposed cohorts based on MDE status at baseline interview and then these depressed and non-depressed cohorts were followed for 12 years to compare the incidence of migraine.

3.8 Subjects

The study sample was selected from 17,276 participants in the 1994/1995 NPHS longitudinal panel. Respondents younger than 12 years (n=2,022) in 1994/1995 were excluded. The final study sample size was 15,254.

3.9 Cohort definitions

In the first retrospective analysis, as noted above, respondents with MDE in 1994/1995 were excluded (n=849) from the analysis for incident MDE, see Figure 3.1. Respondents that were missing information about MDE status at baseline were also excluded (n=1,230). The remaining subjects made up the non-depressed cohort (n=13,175). By the next cycle, 1,360 respondents from this non-depressed cohort were missing information about MDE status (thereby providing no information about MDE risk). Exclusion of these respondents left 11,815 at risk for developing MDE in 1996/1997, see Figure 3.1.

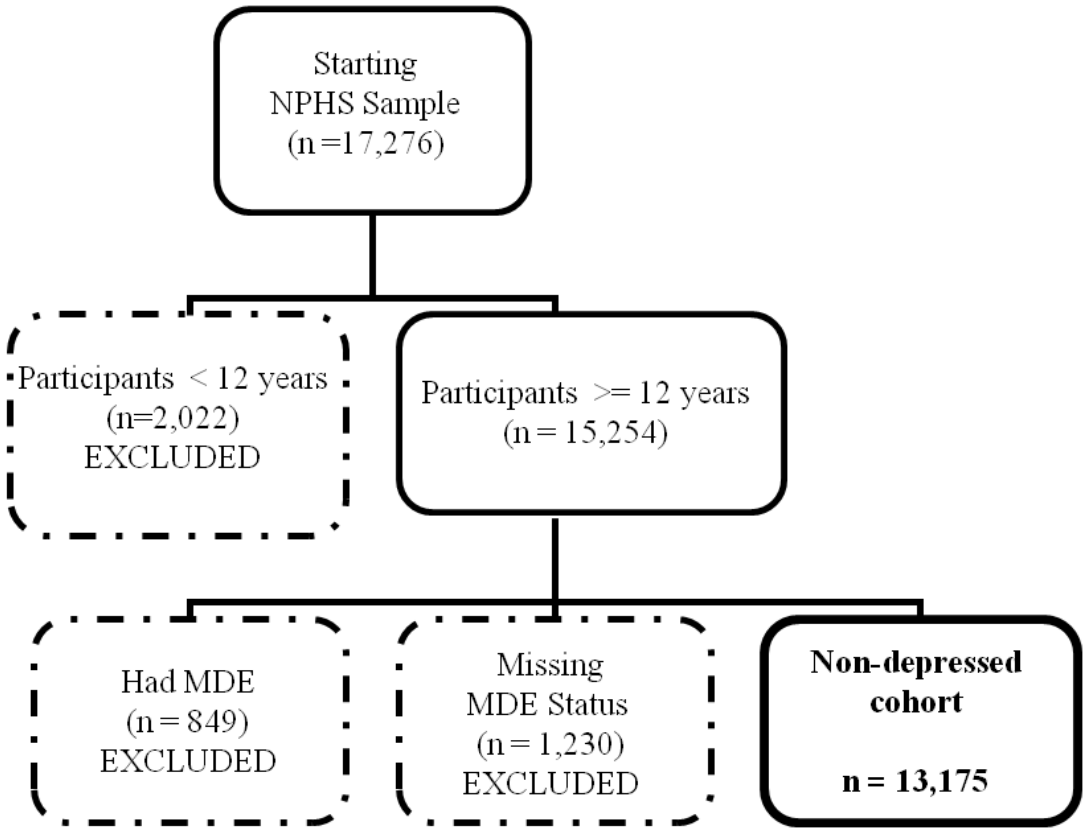

Figure 3.1 Flowchart of the 1994/1995 non-depressed cohort

Similarly, in the second retrospective analysis, respondents with migraine in 1994/1995 were excluded (n=1,147) from the analysis for incident migraine, see Figure 3.2. Respondents were included in the analyses only if they had complete information about migraine status at baseline. Therefore, those respondents that were missing information about migraine status were also excluded (n=23).The remaining subjects made up the non-migraineur cohort (n=14,084) at risk for developing migraine during the following 12 years. However, there were n=1,264 who provided no information about risk of migraine

since they had missing data at the subsequent cycle, leaving 12,820 for inclusion in the analysis.

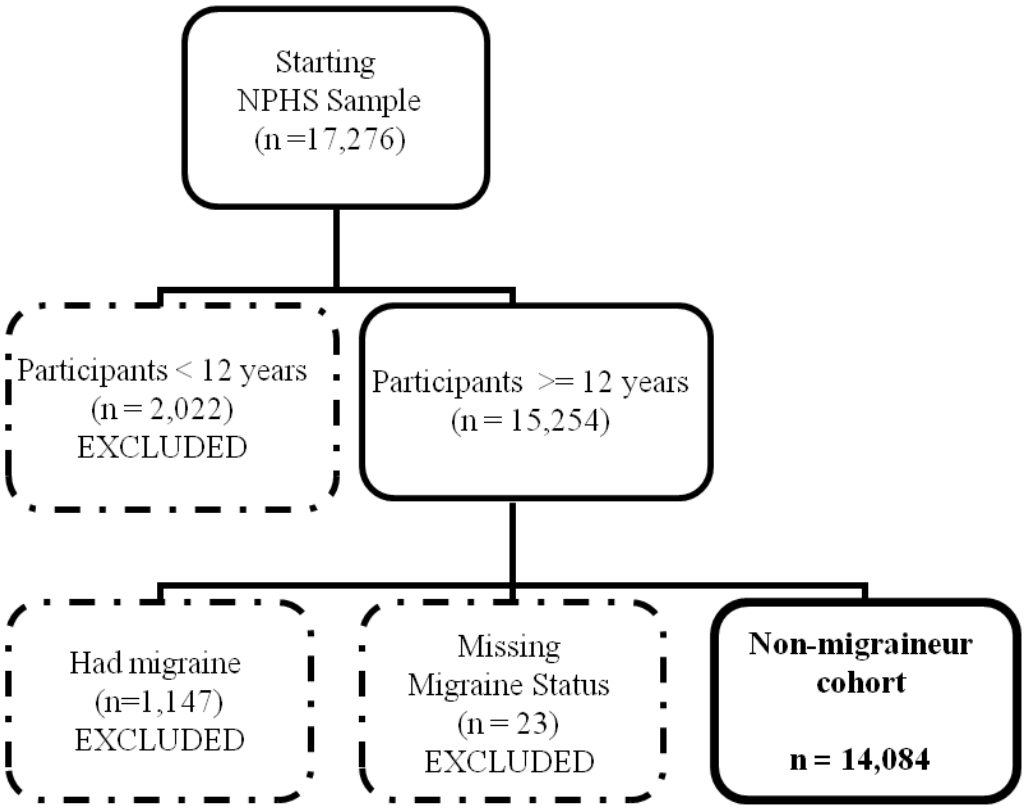

Figure 3.2 Flowchart of the 1994/1995 non-migraineur cohort

To achieve the objectives involving the estimate of cumulative incidence, additional exclusion criteria were applied. Cumulative incidence represents the proportion of a closed population at risk for a disease that develops the disease during a specified interval (Porta & International Epidemiological Association 2008). In this study, the closed population at

risk for developing MDE (or migraine) contained only subjects followed for the entire duration of follow-up (n=7,029). Therefore, any respondents who left and came back, died, or missed a cycle were excluded in the calculation of cumulative incidence. In those parts of the analysis using proportional hazards modelling, respondents who left the sampling frame or were lost to follow-up were censored from the analysis after their most recently available observation.

In the estimation of the cumulative incidence of migraine, members that left the non-migraineur cohort for any period during the follow-up period were excluded. The remaining subjects with complete follow-up data made up the closed non-migraineurs cohort (n=7,145) of subjects at risk of developing migraine.

3.10 Data management and missing data

Statistics Canada's initial management of the NPHS data included: checking for data entry errors, missing data, and out of range values. This was done prior to releasing the data file made available for this study. During the data editing by Statistics Canada, missing or incorrect values were categorized as: *not stated*, *refusal*, and *do not know* by Statistics Canada. For this thesis project, additional data checking, prior to the formal statistical analysis, was performed at the Prairie Regional Data Centre Calgary, by examining cross-tabulations to check for out of range values or any other anomalies. No errors such as out of range or anomalous values were identified during this process.

3.11 Statistical analysis

3.11.1 Preliminary analysis

Data screening and examination of descriptive statistics of the study sample were performed before the start of the statistical analysis. Subjects with MDE and migraine or those with missing data pertaining to these variables were identified in each of the seven NPHS cycles. Subjects that left the sampling frame and therefore did not provide full information about MDE or migraine at each cycle were identified. These subjects were excluded during the estimation of cumulative incidence and right censored during proportional hazards modelling (see below).

3.11.2 Cross-sectional analysis

In the cross-sectional analysis, logistic regression was used to obtain the unadjusted estimates of odds ratios for the cross-sectional association of migraine and MDE. These estimates were calculated for each of the seven cycles of the NPHS (1994/1995 to 2006/2007). It is unusual to use logistic regression to generate estimates of an unadjusted odds ratio. This approach was employed in the current study, however, since the alternative methods available in the computer program, STATA 11.0 (the “epitab” commands) were not compatible with the use of replicate weights in the bootstrap procedure used for variance estimation. Although, not a primary goal of this study, the prevalence of migraine

at each cycle of the NPHS is presented as these results have not yet been reported in the literature.

3.11.3 Longitudinal analysis

As described above, two separate analyses were carried out to examine the bidirectional association between MDE and migraine. In Part A of the longitudinal analysis, migraine was treated as the exposure and risk of MDE was the outcome. Only the non-depressed cohorts described earlier were used for this part of the analysis, as described above. In part B of the longitudinal analysis, MDE was treated as the exposure and risk of migraine was the outcome. Each condition under evaluation was assessed using the same methods. The methods of longitudinal analysis will therefore only be described here once (for incident MDE). The method of analysis was repeated in its entirety for the assessment of incident migraine.

3.11.3.1 Univariate analysis

First, cumulative incidence proportions of MDE were calculated among the fixed cohort with complete data in all seven cycles. The numerator in the calculation was the number of respondents with MDE at any interview. The denominator included only the fixed cohort with complete data collection (n=7,029). Cumulative incidence proportions of MDE were calculated for each interval period between baseline and follow-up points.

3.11.3.2 Bivariate analysis

In the bivariate analysis, an unadjusted odds ratio for incidence of MDE in subjects with migraine was calculated. The computer program, STATA 11.0, was not able to provide bootstrapped and weighted estimates of risk ratios, therefore incidence odds ratios (OR) obtained from logistic regression (as described above) were used to approximate these risk ratios. As the incidence of both MDE and migraine is relatively low in the general population, the rare disease assumption is applicable. The rare disease assumption allows the incidence odds ratio to approximate the risk ratio when the disease of interest is rare (Porta & International Epidemiological Association 2008).

3.11.3.3 Stratified analysis

An unadjusted estimate of association may be misleading if the association is affected by confounding or effect modification. As the third step of the analysis, the association between MDE and migraine was stratified by levels of demographic, psychosocial, and clinical variables to identify confounding or effect modification. The estimates of 12 year cumulative incidence of MDE, odds ratios, and the corresponding 95% confidence intervals were calculated and compared to assess confounding or effect modification. Confounding is the "distortion of the apparent effect of an exposure on risk brought about by the association with other factors that can influence the outcome" (Porta & International Epidemiological Association 2008). Effect modification occurs when the

association between an exposure and outcome is different in different strata defined by a third factor. The process of "stratification is used to evaluate both confounding and effect modification, to control the former, and to describe the latter (p.313)" (Hennekens et al. 1987). When stratum-specific relative risks were similar with each other and the odds ratios (stratum-specific and pooled) were different from the unadjusted odds ratio, the stratified analysis was interpreted as providing evidence of confounding. If stratum-specific relative risks were different from each other, this was taken as evidence of effect modification.

3.11.3.4 Proportional hazards modeling

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

and therefore leave the at risk cohort). The proportional hazards models were fit as generalized linear models of the binomial family with a complementary log-log function (Jenkins 1997)**.** The proportional hazards assumption was evaluated using a likelihood ratio test for the significance of time-by-exposure (migraine) interactions.

Two types of analysis were performed to obtain unadjusted estimates of the effect of migraine on MDE incidence. First, migraine was treated at a time-invariant factor, so that migraine status at baseline (1994/1995) determined whether a respondent was in the exposed or in the non-exposed cohort. Second, migraine was treated as time-varying factor so that migraine status at the start of each risk interval determined whether a respondent was in the exposed or in the non-exposed cohort during that interval. Since some people classified as not having migraine at baseline subsequently developed migraine, the time-varying definition is likely to involve less misclassification than the time-invariant definition. In the calculation of the adjusted estimates of the effect of migraine on MDE the covariates were included in the models, where possible, as time-varying characteristics. Some variables (e.g. the measure of social support) were only used at the first cycle and could therefore not be treated as time-varying characteristics.

In first stage of proportion hazard modelling age and sex were added to the unadjusted model. Then, in a stepwise modelling process, the potential confounding variables were added one at time to the models adjusted by age and sex. Additional models were created that included adjustment for more than one variable at a time. In the

development of these more complex models, decisions about whether to include certain variables were determined by evidence of their possible confounding roles in the simpler models. In order to develop more broadly predictive models, variables that did not act as confounders were retained in some of the models if they were significantly associated with MDE incidence. Similar procedures were used in the analysis concerned with MDE as a risk factor for migraine.

3.11.4 Estimation procedures for NPHS data

As noted above, the NPHS used a multistage sampling procedure that resulted in unequal selection probability and potential correlations of measures within sampling units. To account for these design effects, data were weighted using replicate sampling weights provided by Statistics Canada using a recommended bootstrap procedure (Statistics Canada 2009b). The bootstrap procedure was used to calculate the variance of all estimates and in the assessment of statistical significance. In this study, 500 replicate bootstraps were used for each estimate, as recommended. All analysis and bootstrapping procedures were performed in STATA, version 11.0 (Stata Corporation 2010).

Chapter Four: Results

4.1 Description of the study sample

The demographic and socioeconomic characteristics of the participants at the baseline interview in 1994/1995 are described in Table 4.1. There were slightly more females than males in the study population. In 1994/1995, those between the ages of 26 to 45 accounted for the largest proportion of participants followed by those over the age of 46. A majority of the participants in 1994/1995 were either married or living common law.

Table 4.1 Demographic status and socioeconomic characteristics of the NPHS participants in 1994/1995 (n=15,254)

	% (95% CI)†
Sex	
Males	49.2 (49.2-49.2)
Females	50.8 (50.8-50.9)
Age	
12 – 25	23.0 (22.8-23.3)
26 – 45	40.0 (39.6-40.3)
46 +	37.0 (36.8-37.3)
Marital status	
Married/common-law	59.0 (58.2-59.9)
Single/never-married	28.9 (28.3-29.6)
Widowed/separated/divorced	12.1 (11.6-12.7)
Income (low/middle)	17.9 (17.1-18.7)
Some post secondary education	48.2 (47.2-49.3)

†Above percentages (%) represent estimates of overall sample (n=15,254), thus % for the row, not the column

Among the 15,254 respondents, 7.1% (CI 6.6-7.6) reported having migraine and 5.6% (CI 5.1-6.0) were identified as having MDE (Table 4.2). In 1994/1995, close to 50% of respondents in this study population reported having experienced at least one traumatic event during childhood and over 35% had a significant level of stress. Current smokers (daily and occasional) accounted for almost 30% of respondents and approximately 50% of the respondents had at least one chronic health condition other than migraine or MDE.

Table 4.2 Health characteristics of the NPHS respondents in 1994/1995

	n = 15,254 % (95% CI) †
Health status	
MDE	5.6 (5.1-6.0)
Migraine	7.1 (6.6-7.6)
Chronic health condition	47.7 (46.6-48.7)
Obese (BMI>30)	12.7 (12.0-13.5)*
Pain intensity (moderate/severe)	11.9 (11.0-12.4)*
Injured in past 12 months	17.3 (16.5-18.1)*
Physical inactivity	58.4 (57.3-59.5)*
Currently smoking	29.3 (28.5-30.2)
Family history of depression (2004/2005)	19.8 (18.8-20.9)**
Medications used in past month	
Anti-depressant	2.9 (2.5-3.2)*
Analgesic/narcotic (Demerol, codeine, morphine)	4.3 (3.9-4.7)*
Pain/anti-inflammatory (Tylenol/aspirin)	61.5 (60.4-62.6)*
Psychosocial characteristics	
Low self-esteem	32.5 (31.5-33.4)
Low social support	16.8 (15.9-17.7)
Low sense of mastery	24.7 (23.8-25.6)
Stress	36.9 (35.9-37.9)
Childhood trauma	49.0 (47.8-50.1)

†Above percentages (%) represent estimates of overall sample (n=15,254), thus % for the row, not the column

*These variables are included for descriptive purposes. Details about their measurement can be found in the NPHS survey documentation

**Family history of depression is the only one of these measures not assessed at baseline.

4.2 MDE as outcome

4.2.1 MDE status of the respondents at baseline

Among the 15,254 participants eligible for the analysis, 8.1% were missing information required to classify their MDE status in 1994/1995 and were excluded from the estimates pertaining to MDE as an outcome (Table 4.3).

Among the 14,024 remaining respondents who provided full information for the establishment of MDE status in 1994/1995, 6.1% were scored at the 90% positive predictive value level by CIDI-SF thereby classifying them with MDE. The 93.9% left over respondents (13,175) did not have MDE in 1994/1995 and they comprise the non-depressed cohort and will be part of the longitudinal analysis of MDE as an outcome (Table 4.3).

Table 4.3 MDE status of the NPHS respondents in 1994/1995

	Missing data about baseline MDE status % (n)	No MDE % (n)	MDE % (n)
Entire sample, (n=15,254)	8.1% (1,230)	86.4 % (13,175)	5.6 % (849)
Limited to those without missing data about baseline MDE status, (n=14,024)	-	93.9 % (13,175)	6.1 % (849)

4.2.2 Loss to follow-up and missing data for primary MDE

The 12 year cumulative loss to follow-up of the study cohort (n=15,254) between 1994/1995 and 2006/2007, was 23.0%. During this same 12 year period, 2,024 respondents from the original study cohort had died. As stated in the Section 3 (missing data), the respondents with missing data for either primary variables (MDE and migraine) were excluded from the corresponding analyses of cumulative incidence and right censored during proportional hazards modeling. Missing data for MDE is summarized in Table 4.4.

Table 4.4 Loss to follow-up of study cohort and missing data for MDE, by cycle (n=15,254)

	Loss to follow-up (Not able to trace)*	Population exclusion		Missing (Not stated/ partial responses)**	With information about MDE status
		Dead*	Institutionalized**		
1994/1995	0.0%	0.0%	0.0%	8.1%	91.9%
1996/1997	6.6%	1.9%	0.4%	2.8%	88.3%
1998/1999	11.4%	4.0%	0.7%	2.6%	81.3%
2000/2001	15.4%	6.4%	0.9%	4.1%	73.3%
2002/2003	19.5%	8.6%	1.1%	4.5%	66.3%
2004/2005	22.7%	11.0%	0.9%	3.6%	61.8%
2006/2007	23.0%	13.3%	1.0%	7.0%	55.8%

* Cumulative proportion.
** Non-cumulative proportion. The proportion of institutionalized respondents is not cumulative since respondents could leave this categorization via death.

4.2.3 Cross-sectional association of migraine and MDE

In 1994/1995, the prevalence of MDE among respondents with migraine was 14.2% compared to only 4.9% for respondents without migraine, approximately a threefold difference (OR 3.2 CI 2.5-4.1). This pattern was repeated at each cycle (Table 4.5).

Table 4.5 Unadjusted prevalence estimates of the association between MDE and migraine at each cycle

	No Migraine % (95% CI)	Migraine % (95% CI)	OR (95% CI)*
1994/1995	4.9 (4.4-5.4)	14.2 (11.7-16.7)	3.2 (2.5-4.1)
1996/1997	4.1 (3.6-4.6)	11.6 (9.0-14.1)	2.9 (2.2-3.8)
1998/1999	3.9 (3.3-4.5)	9.1 (6.1-12.0)	3.2 (2.4-4.3)
2000/2001	3.7 (3.1-4.3)	10.7 (7.7-13.7)	3.1 (2.4-4.1)
2002/2003	4.2 (3.6-4.9)	11.1 (8.0-14.2)	3.0 (2.2-3.9)
2004/2005	4.3 (3.6-5.0)	9.4 (6.4-12.4)	2.9 (2.1-4.1)
2006/2007	4.8 (4.1-5.4)	10.5 (7.5-13.4)	2.9 (2.1-4.1)

*Odds Ratio (OR) obtained via logistic regression

4.2.4 Longitudinal analysis of MDE as an outcome

4.2.4.1 Incidence of MDE

This section presents the incidence proportions of MDE at each of the six follow-up intervals beginning with 1994/1995 to 1996/1997. In 1994/1995, 86.4% of the sample (13,175) reported they did not have MDE (Table 4.4). In 1996/1997, 1360 were missing

information about MDE status and were excluded from the calculation of incidence of MDE in 1996/1997. Among remaining 11,815 respondents at risk for developing MDE in 1996/1997, 3.5% reported MDE at the 1996/1997 follow-up interview. At the second follow-up interview in 1998/1999, the 'at risk' group diminished as respondents with MDE in either 1994/1995 or 1996/1997 were not included in the denominator, nor were respondents with missing information about MDE status at any of the three time points (1994/1995, 1996/1997 or 1998/1999). The two year incidence of MDE during the period between 1996/1997 and 1998/1999 was 3.2%. The incidence of MDE slightly diminished at each subsequent follow-up period (Table 4.6) corresponding to more time spent in the non-depressed state.

Table 4.6 Two year incidence proportions of MDE, by cycle

	Respondents at risk for MDE* (n)	Incidence proportion % (95% CI)
1996/1997	11,815	3.5 (3.1-4.0)
1998/1999	10,231	3.2 (2.8-3.6)
2000/2001	8,657	3.0 (2.5-3.4)
2002/2003	7,305	2.9 (2.3-3.4)
2004/2005	6,284	3.1 (2.5-3.7)
2006/2007	5,334	1.8 (1.4-2.2)

* Respondents without MDE at any prior cycle

4.2.4.2 Cumulative incidence of MDE

This section presents the cumulative incidence proportion of MDE during the 12 year study period. The denominator for this cumulative incidence proportion represents the 7,029 respondents who reported MDE status at every follow-up interview.

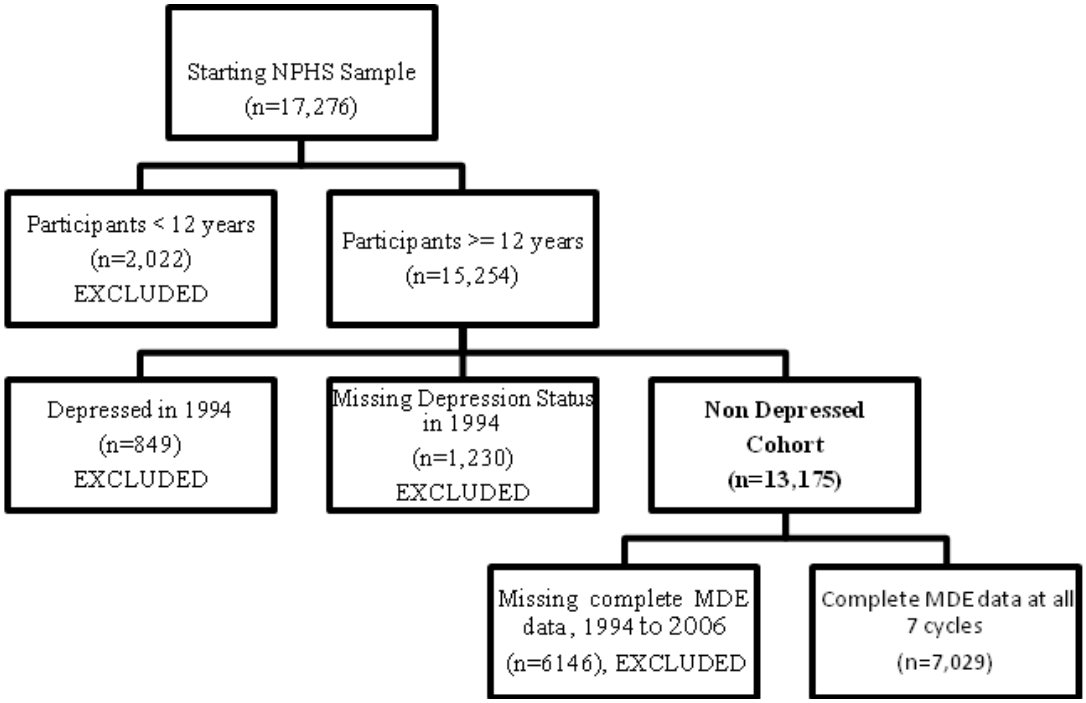

Figure 4.1 Flowchart of the non-depressed cohort at risk for cumulative incidence of MDE

The numerator is the number of respondents with MDE at interview after baseline. During the 12 year follow-up period, 15.2% of respondents had at least one new episode of MDE (Table 4.7).

Table 4.7 Cumulative incidence proportion of MDE among respondents with complete data

	Cumulative incidence calculation	Cumulative incidence proportion of MDE % (95% CI)
1994/1995 to 1996/1997	2 year	3.4 (2.8-4.0)
1994/1995 to 1998/1999	4 year	6.3 (5.6-7.0)
1994/1995 to 2000/2001	6 year	8.8 (8.0-9.6)
1994/1995 to 2002/2003	8 year	11.2 (10.3-12.2)
1994/1995 to 2004/2005	10 year	13.8 (12.7-14.8)
1994/1995 to 2006/2007	12 year	15.2 (14.0-16.2)

4.2.5 Longitudinal association between migraine and incident MDE

4.2.5.1 The unadjusted estimate of the longitudinal association between migraine and incident MDE

As noted above (Table 4.7), the 12 year cumulative incidence of MDE was 15.2%. The 12 year cumulative incidence of MDE among respondents who did not report having migraine in 1994/1995 was 14.6% compared to 22.2% for respondents with migraine (Table 4.8). Hence, during the 12 year follow-up interval, the odds of incident MDE in those with migraine was 70% higher among migraineurs compared to non-migraineurs (Table 4.8). Shorter follow-up intervals yielded similar results (Table 4.9).

Table 4.8 Unadjusted association between migraine and 12 year cumulative incidence of MDE

	12 year cumulative incidence of MDE % (95% CI)	OR (95% CI)
No Migraine	14.6% (13.5-15.8)	1.7 (1.3-2.2)
Migraine	22.2 % (18.0-26.5)	

Table 4.9 Unadjusted association between migraine and incident MDE

	Cumulative incidence of MDE % (95% CI)		OR (95% CI)
	No migraine	Migraine	
2 year	3.2 (2.6-3.8)	6.1 (3.7-8.5)	2.0 (1.2-3.2)
4 year	6.0 (5.2-6.7)	11.1 (8.0-14.2)	2.0 (1.4-2.8)
6 year	8.4 (7.5-9.2)	14.2 (10.8-17.5)	1.8 (1.3-2.4)
8 year	10.8 (10.0-11.8)	17.4 (13.6-21.2)	1.7 (1.3-2.3)
10 year	13.3 (12.2-14.4)	20.0 (15.9-24.1)	1.6 (1.2-2.2)
12 year	14.6 (13.5-15.8)	22.2 (18.0-26.5)	1.7 (1.3-2.2)

4.2.5.2 Stratified analysis for incident MDE

As stated in section 3.11.3.3, the unadjusted association between migraine and MDE risk was stratified by levels of socio-demographic and health related variables. This section presents a stratified analysis performed to investigate whether the unadjusted

association between MDE and migraine was either modified or confounded by any of the following variables: sex, age, self-esteem, social support, childhood trauma, chronic health conditions, family history of depression, and smoking status. The stratified estimates are presented in Tables 4.10 to 4.12.

As stated in section 3.11.3.3, evidence of effect modification by any of the above variables on the association between migraine and MDE was based on a judgment concerning whether the stratum specific estimates (odds ratios) were different. Confounding was assessed only in circumstances where there was no evidence of effect modification.

The 12 year cumulative incidence of MDE was 25.7% among the female migraineurs and 17.3% among the female non-migraineurs (Table 4.10) with an OR of 1.7 (CI 1.2-2.2). Among males, there was a somewhat smaller OR (1.2, CI 0.6-2.3) for the cumulative incidence of MDE between the migraineurs and the non-migraineurs. However, the stratum specific estimates for sex were deemed not to provide firm evidence of effect modification therefore a pooled (unconfounded) summary estimate for sex (OR 1.5, CI 1.1-2.0) was calculated using logistic regression. The stratified analysis indicates a 20% difference between the unadjusted estimate (OR 1.7) and adjusted estimate (OR 1.5), suggesting that due to the particular mix of subjects included in this study, sex confounded the relationship between migraine and the risk of MDE.

Table 4.10 Summary of the stratified analysis of cumulative incidence of MDE and migraine by sex

	Cumulative incidence proportion	Stratum specific OR, 95% CI	Pooled OR (95% CI)
Male			
No migraine	11.0 % (9.4-12.6)	1.2 (0.6-2.3)*	1.5 (1.2-2.0)**
Migraine	12.7% (6.0-19.4)		
Female			
No migraine	17.3% (15.6-18.9)	1.7 (1.2-2.2)	
Migraine	25.7% (20.4-30.9)		

* Caution in interpretation as wide confidence interval crossing the null value indicates small cell size and lack of precision in this measurement.
** The test for significance of interaction term (migraine*sex) confirmed judgment that stratum specific estimates are not different (p-value=0.39)

Age specific estimates were compared to look for effect modification by this variable (Table 4.11). None was found. Five age strata were first explored, however in these strata, very small cell sizes and wide confidence intervals were found leading to lack of precision. The age categories were therefore collapsed into three-age strata, as previously described. The stratum specific estimate for the youngest age group was lower than the middle (26-45) and oldest (46+) age group however this difference was potentially due to sampling variability as seen by the wide confidence intervals, which also cross the null value. Consequently, a judgment was made that no differences were observed across the three age specific strata hence; there was no evidence of effect modification by age. Although the OR in the youngest group was weaker than that in the other strata, this may

have been due to sampling variability, especially as the direction of effect seemed implausible, despite the weakly significant interaction term, see Table 4.11. As there was deemed to be no strong evidence of effect modification by age, the possibility of confounding by age on the relationship between migraine and MDE was evaluated. As with sex, logistic regression was used to obtain the age-adjusted estimate of effect. The age-adjusted estimate (OR 1.7, CI 1.3-2.2) did not differ from the unadjusted estimate (OR 1.7, 1.3-2.2) indicating no evidence of confounding by age.

Table 4.11 Summary of the stratified analysis of cumulative incidence of MDE by migraine and age

	Cumulative incidence of MDE % (95%CI)			
	No migraine	Migraine	Stratum specific OR (95% CI)**	Pooled OR (95% CI)
Age				
12 - 25	21.4 (18.3-24.4)	16.6 (7.4-25.7)	0.7 (0.4-1.5)*	
26 - 45	15.3 (13.6-17.0)	26.8 (20.1-33.3)	2.0 (1.4-2.9)	1.7 (1.3-2.2)
46 +	9.7 (8.2-11.2)	17.4 (10.1-24.7)	2.0 (1.1-3.4)	

*Caution in interpretation as wide confidence interval crossing the null value indicates small cell size and lack of precision in this measurement.

**The test for significance of interaction term (migraine*age) was weakly significant (p-value=0.04) but was not taken as evidence of effect modification, see text.

This same method of stratified analysis revealed no effect modification or confounding by: income, self-esteem, social support, stress, chronic health conditions or smoking status. The adjusted estimate for family history of depression (OR 1.5) was slightly lower than the unadjusted estimate suggesting family history of depression may be a potential confounder (Table 4.12).

Table 4.12 Summary of the stratified analysis of the cumulative incidence of MDE by migraine and health related factors

	Cumulative incidence MDE, % (95% CI)		Stratum specific OR (95% CI)	Pooled OR (95% CI)
	No Migraine	Migraine		
Income				
Not low income	14.0 (12.7-15.3)	22.0 (17.3-26.7)	1.7 (1.3-2.3)	1.7 (1.3-2.2)
Low income	17.8 (14.3-21.2)	26.7 (14.0-39.3)	1.7 (0.8-3.4)*	
Low self-esteem				
No	13.8 (12.4-15.2)	20.9 (25.6-26.2)	1.6 (1.2-2.3)	1.7 (1.3-2.2)
Yes	16.2 (14.1-18.3)	25.0 (17.2-32.8)	1.7 (1.1-2.7)	
Social support				
Socially supported	14.3 (13.1-15.6)	22.2 (17.6-26.8)	1.7 (1.3-2.3)	1.7 (1.3-2.2)
Lacking support	16.4 (13.0-19.8)	23.2 (11.1-35.4)	1.5 (0.7-3.4)*	
Childhood trauma				
No	10.3 (8.9-11.7)	14.6 (8.9-20.3)	1.5 (0.9-2.4)*	1.7 (1.3-2.2)
Yes	18.3 (16.3-20.2)	28.2 (22.2-34.1)	1.8 (1.2-2.5)	
Chronic health conditions				
No	14.3 (12.8-15.8)	18.8 (11.6-26.0)	1.3 (0.8-2.3)*	1.6 (1.3-2.2)
Yes	15.0 (13.3-16.7)	24.0 (18.7-29.4)	1.8 (1.3-2.5)	
Current Smoker				
No	12.8 (11.5-14.1)	21.1 (16.3-26.0)	1.3 (1.3-2.5)	1.6 (1.2-2.2)
Yes	20.1 (17.6-22.7)	25.0 (16.7-33.3)	1.8 (0.8-2.1)*	
Family history depression				
No	12.6 (11.4-13.9)	24.1 (20.7-27.5)	1.3 (0.9-1.9)*	1.5 (1.1-1.9)
Yes	16.0 (11.6-20.3)	35.0 (25.2-44.8)	1.7 (1.0-2.8)	

*Caution in interpretation as wide confidence interval crossing the null value indicates small cell size and lack of precision in this measurement.

4.2.5.3 Proportional hazard modeling for incident MDE

This section will present the results for the proportional hazard modeling for grouped time data. The proportional hazards assumption was evaluated using a likelihood ratio test for time-by-exposure interactions (migraine by each of the five indicator variables for the risk intervals). No violation of the proportional hazards assumption was identified for any of the five likelihood ratio tests.

4.2.5.3.1 Unadjusted HR based on time-invariant exposure

In the previous section, the association between migraine and MDE risk was identified by an odds ratio of 1.7 (CI 1.3-2.2) in an analysis based on cumulative incidence, see Table 4.8. The unadjusted OR and unadjusted HR are expected to be similar, however, as the HR is calculated from a larger at risk population (both partial and full responses are included), the HR may be a more precise measure. Using time-invariant (baseline only) migraine measurement, the unadjusted HR was 1.7 (CI 1.4-2.1), an estimate that is more precise than that arising from the cumulative incidence evaluation, see Table 4.13.

4.2.5.3.2 Unadjusted HR based on time-varying exposure

The unadjusted hazard ratio using the time-varying migraine definition was 2.1 (CI 1.7-2.5), see Table 4.13. Over the entire study period (1994/1995 to 2006/2007), people with migraine had 2.1 times the risk of developing MDE compared to those without

migraine. The adjusted HRs obtained in the following proportional hazard models included the time-varying migraine variable as the exposure, see Table 4.13.

Table 4.13 Comparison of unadjusted associations for incident MDE from logistic regression and proportional hazard models

Migraine (exposure)	Unadjusted risk ratio (95% CI) for MDE
Time-invariant (1994/1995)	OR 1.7 (1.3 - 2.2)
Time-invariant (1994/1995)	HR 1.7 (1.4 - 2.1)
Time-varying (1994/1995 to 2006/2007)	HR 2.1 (1.7 - 2.5)

4.2.5.3.3 Assessment of independent risk factors for incident MDE

To confirm that each of the additional variables was indeed a risk factor for MDE, one at a time, each variable were included in a proportional hazard model predicting MDE. This was done because in order for a variable to be a confounder it needs to both an independent risk factor for MDE and associated with migraine. These one at a time assessments of each of the potential confounders confirmed each variable to be an independent risk factor for MDE (Table 4.14).

Table 4.14 Comparison of independent risk factors for MDE

	HR (95% CI)
Female sex	1.7 (1.4-1.9)
Youngest age group (12-25) compared to oldest age group (46+)	2.2 (1.8-2.6)
Middle age group (26-45) compared to oldest age group (46+)	1.8 (1.5-2.1)
Low income	1.4 (1.1-1.7)
Lower self-esteem	1.4 (1.1-1.7)
Lacking social support	1.4 (1.0-1.8)
Childhood trauma	2.1 (1.8-2.4)
Chronic health conditions	1.3 (1.2-1.5)
Current smoker	1.6 (1.4-1.9)
Family history of major depression	2.1 (1.8-2.5)

4.2.5.3.4 Assessment of potential effect modification and confounding by additional variables

In this section, potential effect modifying or confounding variables were assessed using proportional hazard modeling. In the stratified analyses, each extraneous variable was assessed one at a time and when measured at baseline, none of the additional variables acted as effect modifiers. Consistent with the stratified analysis, only sex and family history of depression were identified as possible confounders.

4.2.5.3.4.1 Assessment of effect modification for incident MDE

Wald tests of the significance of interaction terms between migraine and each covariate listed in Table 4.15 were assessed. No interactions between the identified covariates and migraine were found, confirming the results from the stratified analysis that none of the additional variables were effect modifiers.

4.2.5.3.4.2 Assessment of confounding for incident MDE

This section presents the adjusted hazard ratios for MDE. The potential time-varying confounders (low income and chronic health conditions) and time-invariant confounders (sex, age, self esteem, social support, childhood trauma, family history of depression) listed in Table 4.15 were first evaluated one at a time.

Table 4.15 Adjusted hazard ratios for MDE risk

	Adjusted HR (95% CI)
Unadjusted Model	*2.1 (1.7-2.5)*
Female sex	1.9 (1.6-2.3)
Age	2.0 (1.7-2.4)
Low income	2.1 (1.7-2.5)
Lower self-esteem	2.1 (1.6-2.7)
Lacking social support	2.1 (1.0-1.8)
Childhood trauma	2.0 (1.6-2.4)
Chronic health conditions	1.9 (1.6-2.3)
Family history of major depression	1.8 (1.5-2.2)

The first model included adjustment only for sex (Table 4.15). The cumulative hazard functions for four groups in the sex-adjusted model were plotted to show differences in the risk trajectories of MDE. The four groups described in this model are: men without migraine, men with migraine, women without migraine and women with migraine (Figure 4.2). In this graph, we see that women with migraine have the highest risk of developing MDE. In addition, both women and men with migraine have a higher risk of developing MDE than either women or men without migraine.

No evidence of age-group by migraine interactions were identified in this analysis, providing additional confirmation that age is not a modifier of the migraine-MDE association. This result supports decisions concerning this potential interaction in the cumulative incidence analysis.

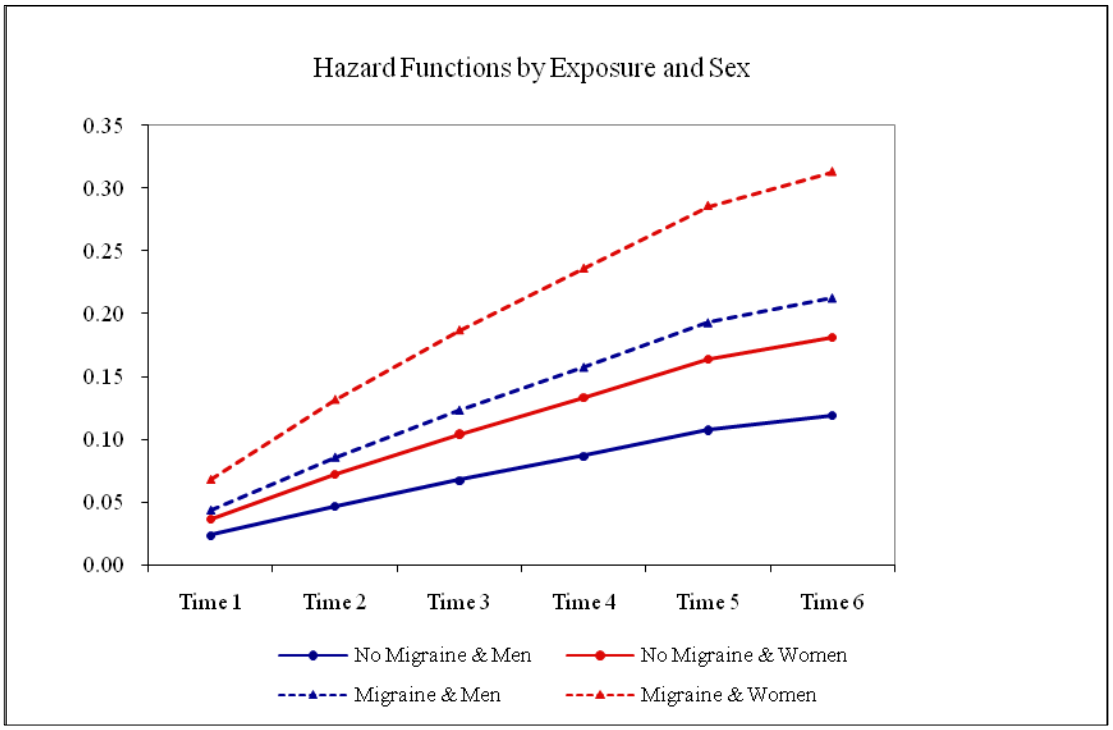

Figure 4.2 Cumulative hazard functions for MDE by migraine and sex

The hazard ratio and corresponding confidence intervals for the sex-adjusted model were lower than the hazard ratio and corresponding confidence intervals from unadjusted model (Table 4.15) providing evidence of confounding and confirming the results of the stratified analysis. Age did not appear to be an effect modifier or confounder when the age adjusted HR (Table 4.15) was compared to the unadjusted HR however simultaneous confounding was found when sex and age were combined in a multivariate model (see next

section). Also consistent with the stratified analysis, there was some evidence that family history may act as a confounding variable (Table 4.15).

Adjusted hazard ratios from one at time models adjusting for income, self-esteem, social support, childhood trauma, and smoking status individually did not differ from the unadjusted hazard ratio or corresponding confidence intervals therefore these variables were not included in the stepwise multivariate modeling process.

4.2.5.3.5 Multivariate proportional hazards modeling for incident MDE

A stepwise process was utilized for the adjustment for the potential confounders (sex, age, chronic health conditions, and family history of depression) in the multivariate proportional hazards modeling. The adjusted hazard ratio for incident MDE (1.8, CI 1.5-2.1) from the age and sex adjusted model (Table 4.16) was lower than both the unadjusted HR (2.1, CI 1.7-2.5) and the models adjusting for sex (1.9, CI 1.6-2.3) and age (2.0, CI 1.7-2.4) in isolation (Table 4.15), therefore both were retained in the for the subsequent model.

Table 4.16 Adjusted (sex and age) model for MDE risk

	HR (95% CI)
Migraine (exposure)	*1.8 (1.5 – 2.1)*
Female	1.6 (1.4 – 1.9)
Age (0 = 46+, 1 = 12-25)	2.2 **(**1.8 – 2.7**)**
Age (0 = 46+, 1 = 26-45)	1.7 **(**1.5 – 2.0**)**

In the next step, the chronic health conditions variable was added to the model. The adjusted hazard ratio (1.6, CI 1.3-1.9) from the model containing sex, age, and chronic health conditions (Table 4.17) was lower than the unadjusted and the sex and age only model.

Table 4.17 Adjusted model (sex, age, and chronic health conditions) for MDE risk

	HR (95% CI)
Migraine (exposure)	*1.6 (1.3 – 1.9)*
Female	1.6 (1.4 – 1.8)
Age (0 = 46+, 1 = 12-25)	2.4 **(**2.0 – 2.9**)**
Age (0 = 46+, 1 = 26-45)	1.9 **(**1.6 – 2.2**)**
Chronic health conditions	1.4 **(**1.2 – 1.6**)**

The addition of family history of depression to the sex and age adjusted (HR 1.6, CI 1.3-2.0) model yielded similar results (Table 4.18).

Table 4.18 Adjusted model (sex, age, and family history of depression) for MDE risk

	HR (95% CI)
Migraine (exposure)	*1.6 (1.3-2.0)*
Female	1.6 (1.3-1.9)
Age (0 = 46+, 1 = 12-25)	2.0 (1.6-2.4)
Age (0 = 46+, 1 = 26-45)	1.5 (1.3-1.9)
Family history of depression	1.9 (1.6-2.2)

Finally, the inclusion of age, sex, chronic health conditions, and family history of depression yielded a hazards ratio of 1.4 (CI 1.2-1.8) (Table 4.19) different from the unadjusted HR (2.1 CI 1.7-2.5) (Table 4.15).

Table 14.19 Adjusted (sex, age, chronic health conditions and family history of depression) model for MDE risk

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

Results from multivariate proportional hazard modeling in the assessment of confounding indicate four variables confound the relationship between MDE and migraine. Respondents with migraine were 40% more likely to develop MDE compared to those without migraine even after adjusting for sex, age, chronic health conditions, and family history of depression (Table 4.20).

Table 4.20 Model comparison for MDE risk

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

4.3 Migraine as outcome

4.3.1 Migraine status of the respondents at baseline

Among the 15,254 respondents eligible for the analysis, only 0.2% were missing information required to classify their migraine status in 1994/1995 and were excluded from this part of the study (Table 4.21). Among the 15,231 remaining respondents who provided full information for the establishment of migraine status in 1994/1995, 1147 respondents (7.5%) indicated they had been diagnosed by a health professional with migraine. The remaining 14,084 respondents (92.3%) that did not have migraine in 1994/1995 comprise the non-migraine cohort.

Table 4.21 Migraine status of the NPHS respondents in 1994/1995

	Missing data about baseline migraine status % (n)	No Migraine % (n)	Migraine % (n)
Entire sample (n=15,254)	0.2% (23)	92.3% (14,084)	7.5% (1147)
Limited to those without missing data about baseline migraine status (n=15,231)	-	92.5% (14,084)	7.5% (1147)

4.3.2 Loss to follow-up and missing data for migraine variable

The cumulative loss to follow-up (attrition) for the entire sample (n=15,254) was 23.0%. By the end of the study period 2024 participants had died. The cumulative proportion of missing data associated with migraine status was 0.8% (Table 4.22).

Table 4.22 Loss to follow-up of study cohort and missing data for migraine, by cycle (n=15,254)

Year	Loss to Follow-up (Not able to trace) *	Population based exclusions		Missing Migraine data (Refusal or not stated)**	Proportion with information about migraine
		Dead*	Institutionalized**		
1994/1995	0.0%	0.0%	0.0%	0.2%	99.8%
1996/1997	6.5%	1.9%	0.4%	0.1%	91.1%
1998/1999	11.3%	4.0%	0.7%	0.1%	83.8%
2000/2001	15.4%	6.4%	0.9%	0.5%	76.9%
2002/2003	19.5%	8.6%	1.1%	0.6%	70.3%
2004/2005	22.7%	11.0%	0.9%	0.5%	64.9%
2006/2007	23.0%	13.3%	1.0%	0.8%	62.1%

* Cumulative proportion.

** Non-cumulative proportion. The proportion of institutionalized respondents is not cumulative since respondents could leave this categorization via death.

4.3.3 Cross-sectional analysis of migraine as an outcome

4.3.3.1 Prevalence of migraine at each survey (1994/1995 to 2006/2007)

This section presents the one year prevalence estimates of migraine calculated for each follow-up period. The prevalence of migraine at the initial NPHS interview was 7.5%. The annual prevalence of migraine over the six follow-up cycles ranged from 7.5% to 9.5% (Table 4.23).

Table 4.23 Prevalence of migraine, by cycle

	Sample size	Prevalence of migraine	
	(n)	(n)	% (95% CI)
1994/1995	15321	1147	7.5 (7.1-7.9)
1996/1997	13894	1096	7.9 (7.4-8.3)
1998/1999	12782	1032	8.1 (7.0-8.5)
2000/2001	11732	1082	9.2 (8.7-9.7)
2002/2003	10721	1024	9.6 (9.0-10.1)
2004/2005	9893	934	9.4 (8.9-10.0)
2006/2007	9460	879	9.3 (8.7-9.9)

In the 1994/1995 baseline survey, the overall prevalence of migraine in the NPHS data was 9.8% (9.0-10.6) for women and 4.4 % (3.6-5.0) for men. The prevalence of

migraine among women was approximately three times that of men at each NPHS follow-up period (Table 4.24).

Table 4.24 Prevalence of migraine by sex and cycle

	Men % (95% CI)	Women % (95% CI)	OR (95% CI)
1994/1995	4.4 (3.6-5.0)	9.8 (9.0-10.6)	2.4 (2.0-2.9)
1996/1997	4.2 (3.5-4.9)	11.5 (10.6-12.4)	2.9 (2.4-3.6)
1998/1999	4.2 (3.4-5.0)	11.9 (11.0-12.8)	3.1 (1.5-3.7)
2000/2001	4.8 (4.0-5.5)	13.6 (12.5-14.7)	3.2 (2.6-3.8)
2002/2003	4.9 (4.1-5.8)	13.7 (12.6-14.9)	3.0 (2.5-3.7)
2004/2005	4.5 (3.7-5.3)	14.0 (12.7-15.4)	3.4 (2.8-4.3)
2006/2007	4.6 (3.7-5.5)	13.3 (12.1-14.5)	3.2 (2.5-4.0)

4.3.3.2 Cross-sectional association between migraine and MDE

In 1994/1995, the prevalence of migraine among respondents with MDE of 18.6% (15.4-21.8) was 3.2 times that of respondents without MDE. This pattern was repeated at each cycle (Table 4.25). The odds ratios representing the cross-sectional association between migraine and MDE were presented in Table 4.5, but are repeated here for consistency of reporting.

Table 4.25 Unadjusted associations between migraine and MDE each cycle

	Prevalence of migraine		
	No MDE % (95% CI)	MDE % (95% CI)	OR (95% CI)
1994/1995	6.6 (6.1-7.2)	18.6 (15.4-21.8)	3.2 (2.5-4.1)
1996/1997	4.0 (3.3-4.6)	10.8 (7.8-13.8)	2.9 (2.2-3.8)
1998/1999	8.2 (7.4-9.0)	18.0 (12.5-23.5)	3.2 (2.4-4.3)
2000/2001	9.3 (8.4-10.1)	24.1 (17.8-30.4)	3.1 (2.4-4.1)
2002/2003	9.2 (8.2-10.2)	22.2 (16.4-27.9)	3.0 (2.2-3.9)
2004/2005	9.3 (8.3-10.4)	19.2 (13.3-25.1)	2.9 (2.1-4.1)
2006/2007	8.9 (7.9-9.8)	22.4 (15.7-29.3)	2.9 (2.1-4.1)

4.3.4 Longitudinal analysis of migraine as an outcome

4.3.4.1 Incidence of migraine at each cycle

This section presents the incidence proportions of migraine at each follow-up interval. In 1994/1995, 92.3% of the sample (14,084) reported they did not have migraine (Table 4.6). In 1996/1997, 1264 were missing information about migraine status and were excluded from the calculation for incident migraine in 1996/1997. Among the remaining 12,820 respondents at risk, 3.1% reported migraine at the 1996/1997 follow-up interview. The two year incidence of migraine during the period between 1996/1997 and 1998/1999

was 2.1%. The incidence of migraine diminished slightly at each subsequent follow-up period (Table 4.26).

Table 4.26 Two year incidence proportion of migraine, by cycle

	Respondents at risk (n)	Incidence proportion % (95% CI)
1996/1997	12,820	3.1 (2.7-3.5)
1998/1999	11,282	2.1 (2.4-2.5)
2000/2001	9,813	2.9 (2.4-3.3)
2002/2003	8,454	2.1 (1.7-2.5)
2004/2005	7,344	1.7 (1.3-2.2)
2006/2007	6,548	1.5 (1.1-1.8)

4.3.4.2 Cumulative incidence of migraine

This section presents the cumulative incidence proportion of migraine during the 12 year study period. Results show 12.4% of respondents had a new diagnosis of migraine during the 12 year follow-up period (Table 4.27).

Table 4.27 Cumulative incidence proportion of migraine among respondents with complete data

	Cumulative incidence calculation	Cumulative incidence proportion of migraine % (95% CI)
1994/1995 to 1996/1997	2 year	3.0 (2.4-3.6)
1994/1995 to 1998/1999	4 year	5.2 (4.5-5.8)
1994/1995 to 2000/2001	6 year	7.8 (6.9-8.6)
1994/1995 to 2002/2003	8 year	9.6 (8.7-10.5)
1994/1995 to 2004/2005	10 year	11.2 (10.2-12.2)
1994/1995 to 2006/2007	12 year	12.4 (11.5-13.5)

4.3.5 Longitudinal association between MDE and incident migraine

4.3.5.1 The unadjusted estimate of the association between MDE and incident migraine

As noted in Table 4.27, the 12 year cumulative incidence of migraine was 12.4%. The 12 year cumulative incidence of migraine among respondents who did not report having MDE in 1994/1995 was 11.9% compared to 24.7% for respondents with MDE (Table 4.28). Therefore, during the 12 year follow-up interval, the odds of incident migraine in those with MDE was 2.4 times that of respondents without MDE (Table 4.28). Shorter follow-up intervals yielded similar results (Table 4.29).

Table 4.28 Unadjusted association between MDE and cumulative incidence of migraine

MDE status (1994/1995)	12 year cumulative incidence of migraine % (95% CI)	OR (95% CI)
No MDE	11.9% (10.8-12.9)	2.4 (1.8-3.3)
MDE	24.7% (19.2-30.0)	

Table 4.29 Unadjusted association between MDE and cumulative incidence of migraine at each follow-up period

	12 year cumulative incidence of migraine, % (95% CI)		OR (95% CI)
	No MDE	MDE	
2 year	2.8 (2.2-3.4)	7.2 (3.7-10.6)	2.7 (1.5-5.0)
4 year	4.9 (4.2-5.5)	11.1 (7.1-15.2)	2.5 (1.6-3.8)
6 year	7.3 (6.5-8.2)	17.0 (11.9-22.1)	2.6 (1.7-3.8)
8 year	9.0 (8.0-10.0)	21.0 (15.7-26.2)	2.7 (1.9-3.8)
10 year	10.6 (9.6-11.6)	23.2 (17.9-28.5)	2.5 (1.8-3.5)
12 year	11.9 (10.8-12.9)	24.7 (19.2-30.0)	2.4 (1.8-3.3)

4.3.5.2 Association between cumulative incidence of migraine and potential confounders

The 12 year cumulative incidence of migraine in women was three times that of men. People in the younger (12-25) and middle (26-45) age groups had twice the incidence

of migraine compared to the oldest respondents. Other factors contributing to increased risk of migraine included stress, low income, and childhood trauma. Smoking, obesity, and chronic health conditions were not identified as risk factors for increased migraine incidence (Table 4.30)

Table 4.30 Association between cumulative incidence of migraine and possible risk factors

	12 year cumulative incidence of migraine	OR (95% CI)
Sex		
Male	7.2 (6.0-8.3)	3.0 (2.5-6.7)
Female	17.8 (16.0-19.2)	
Age		
12 - 25	17.0 (14.7-19.3)	12 - 25 vs. 46+: 2.4 (1.9-3.1)
26 - 45	14.0 (12.4-15.5)	26 - 45 vs. 46+: 1.9 (1.5-2.4)
46 +	7.8 (6.4-9.2)	
Stress	10.7 (9.6-11.7) 16.7 (14.4-18.7)	1.7 (1.4-2.0)
Low income	11.8 (10.7-12.9) 16.1 (13.1-19.0)	1.4 (1.1-1.8)
Childhood stress	10.7 (9.3-12.2) 13.3 (11.7-14.9)	1.3 (1.1-1.5)
Current smoker	12.3 (11.1-13.6) 13.3 (11.2-15.1)	1.1 (0.9-1.4)
Obese	11.8 (10.6-12.9) 12.6 (9.8-15.5)	1.1 (0.8-1.5)
Chronic health conditions	11.9 (10.5-13.3) 13.3 (11.8-14.9)	1.1 (0.9-1.4)

4.3.5.3 Stratified analysis for incident migraine

A stratified analysis was performed to investigate whether the unadjusted association between MDE and migraine was either modified or confounded by any of the previously identified extraneous variables: sex, age, stress, childhood trauma, income, or family history of major depression. The stratified estimates are presented in Tables 4.31 and 4.32.

Among women with MDE, 28.3% had migraine, and fewer non-depressed women had migraine (16.9%). Among men although there appeared to be a larger difference in the 12 year cumulative incidence between the depressed and non-depressed, however, the small number of men with MDE resulted in a lower level of precision and it was not clear that the stratum specific estimates really differed. As the stratum specific cumulative incidence ratios and confidence intervals were considered uniform, a pooled (unconfounded) summary estimate for sex (OR 2.1, CI 1.5-2.9) was calculated using logistic regression. The 30% difference between the unadjusted estimate (OR 2.4) and the pooled or adjusted estimate (OR 2.1) suggested sex may be distorting the true relationship between MDE and the risk of migraine due to the particular mix of subjects in this study.

Table 4.31 Summary of the stratified analysis of cumulative incidence of migraine and MDE by sex

	Cumulative incidence % (95%CI)	Stratum specific OR (95% CI)	Pooled OR (95% CI)
Male			
No MDE	6.4% (5.3-7.5)	2.7 (1.1-6.5)*	
MDE	15.6% (5.4-25.8)		2.1 (1.5-2.9)
Female			
No MDE	16.9 % (15.2-18.5)	2.0 (1.4-2.7)	
MDE	28.3% (21.8-34.9)		

*Caution in interpretation as wide confidence interval indicates small cell size and lack of precision in this measurement.

No differences were observed between the odds ratios and corresponding confidence intervals of the three age specific strata and the age-adjusted estimate (OR 2.2, CI 1.6-3.1) did not differ from the unadjusted (OR 2.4, CI 1.8-3.3).

Table 4.32 Summary of the stratified analysis of 12 year cumulative incidence of migraine, by MDE and age

	Cumulative Incidence % (95%CI)		Stratum Specific	Pooled
	No MDE	MDE	OR (95% CI)	OR (95% CI)
Age				
12 - 25	15.4 (13.0-17.9)	36.5 (23.9-49.1)	3.1 (1.7-5.7)	
26 - 45	13.7 (12.1-15.3)	19.5 (12.2-27.9)	1.5 (0.9-2.5)*	2.2 (1.6-3.1)
46 +	7.4 (6.0-8.7)	19.7 (9.9-29.4)	3.1 (1.5-6.2)	

*Caution in interpretation as wide confidence interval crossing the null value indicates small cell size and lack of precision in this measurement.

Stratified analysis of the 12 year cumulative incidence estimates revealed no effect modification by income, stress, childhood trauma, or chronic health conditions. Individual confounding of the MDE and migraine risk relationship is possible by stress and childhood trauma as the odds ratios (OR 2.1) for these variables were slightly lower than the unadjusted odds ratio (Table 4.33).

Table 4.33 Summary of the stratified analysis of the 12 year cumulative incidence of migraine by MDE and possible effect modifiers or confounders

	Cumulative Incidence Migraine, % (95%CI)		Stratum Specific OR (95%CI)	Pooled OR (95%CI)
	No MDE	MDE		
Income				
Not low	11.1 (10.0-12.2)	24.6 (18.2-31.1)	2.6 (1.8-3.8)	
Low	15.6 (12.3-18.8)	25.7 (13.1-38.3)	1.9 (0.9-3.9)*	2.4 (1.8-3.4)
Stress				
No	10.2 (9.1-11.3)	21.9 (14.7-29.0)	2.4 (1.6-3.8)	
Yes	16.0 (13.6 -18.4)	27.0 (18.8-35.3)	1.9 (1.2-3.1)	2.1 (1.6-3.0)
Childhood trauma				
No	10.6 (9.1-12.1)	15.1 (6.2-24.0)	1.5 (0.7-3.2)*	
Yes	12.5 (10.9-14.1)	24.8 (18.3-31.3)	2.3 (1.6-3.4)	2.1 (1.5-2.9)

* Caution in interpretation as wide confidence interval crossing the null value indicates small cell size and lack of precision in this measurement.

4.3.5.4 Proportional hazard modeling incident migraine

In this section, multiple covariates were evaluated one time in proportional hazard modeling of migraine risk. Before exploring the MDE and migraine risk association using this type of modeling, the proportional hazards assumption was evaluated using likelihood ratio tests for time-by exposure interactions (MDE by each of the five indicator variables for the risk intervals). No violation of the proportional hazards assumption was identified for any of the five likelihood ratio tests.

4.3.5.4.1 Unadjusted HR of migraine risk based on time-invariant exposure

In the previous section, the association between MDE and migraine risk was identified by an odds ratio of 2.4 (CI 1.8-3.3). Using proportional hazard modeling and the time-invariant1994/1995 MDE measurement, the unadjusted HR for the association of MDE and migraine risk was 2.1 (CI 1.7-2.8).

4.3.5.4.2 Unadjusted HR of migraine risk based on time-varying exposure

The unadjusted hazard ratio using time-varying MDE was 1.8 (CI 1.3-2.4). Over the entire study period (1994/1995 to 2006/2007), people with a history of major depression were 80% more likely to develop migraine compared to those without a history of major depression.

Table 4.34 Comparison of unadjusted association from logistic regression and proportional hazard models for migraine

MDE (exposure)	Unadjusted migraine risk ratio (95% CI)
Time-invariant (1994/1995)	OR 2.4 (1.8-3.3)
Time-invariant (1994/1995)	HR 2.1 (1.7-2.8)
Time-varying (1994/1995 to 2006/2007)	HR 1.8 (1.3-2.4)

The unadjusted migraine HR using time-varying MDE (Table 4.34) is represented in the following Figure 4.3.

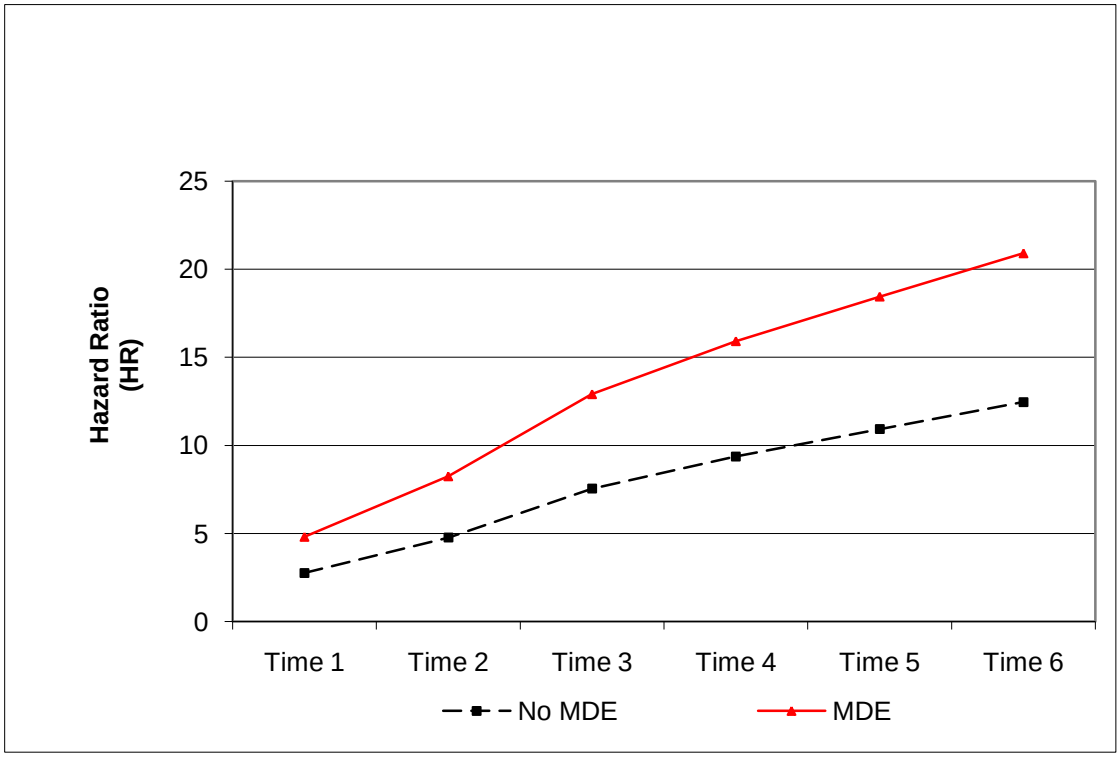

Figure 4.3 Cumulative hazard functions for migraine, by MDE status

4.3.5.4.3 Assessment of independent risk factors for incident migraine

To confirm that each of the additional variables was indeed a risk factor for migraine, each covariate was included in a proportional hazard model predicting migraine in separate models one at a time. These one at a time assessments of each of the potential confounders confirmed each variable to be an independent risk factor for migraine (Table 4.35). Results showed that females are 2.7 times are as likely to develop migraine compared to men. Younger (12-25) and middle (26-45) age groups were found to be twice as likely to develop migraine as the oldest respondents (46+). Respondents with either stress or childhood trauma had higher risk for migraine than those without either of these.

Table 4.35 Hazard ratios for independent risk factors for migraine

	HR (95% CI)
Female sex	2.7 (2.3 - 3.2)
Youngest (12-25) compared to oldest (46+)	2.2 (1.8 - 2.7)
Middle (26-45) to oldest (46+)	1.8 (1.5 - 2.2)
Stress	1.7 (1.5 - 2.0)
Childhood trauma	1.4 (1.2 - 1.7)

4.3.5.4.4 Assessment of potential effect modification and confounding by additional variables on the MDE and migraine risk association

In this section, potential effect modifying or confounding variables were assessed using proportional hazard modeling.

4.3.5.4.5 Assessment of effect modification using proportional hazard modeling for incident migraine

Likelihood ratio tests of the significance of interaction terms between MDE and each covariate were assessed. No interactions between the identified covariates and MDE were found, confirming the results of the stratified analysis.

4.3.5.4.6 Assessment of confounding using proportional hazard modeling for incident migraine

The potential confounders listed in Table 4.36 were then evaluated one at a time in proportional hazards models for migraine risk

Table 4.36 Adjusted hazard ratios from models adjusting for individual potential confounders

	Adjusted HR (95% CI)
Unadjusted Model	*1.8 (1.3 - 2.4)*
Adjusted by sex	1.6 (1.2 - 2.1)
Adjusted by age	1.6 (1.2 - 2.2)
Adjusted by stress	1.6 (1.2 - 2.1)
Adjusted by Childhood trauma	1.2 (0.9 - 1.6)*

* Caution in interpretation as wide confidence interval crossing the null value indicates small cell size and lack of precision in this measurement

Table 4.36 shows the adjusted models. The first model included adjustment for sex as see in Figure 4.4; women were at higher risk of developing migraine compared to men regardless of MDE. The cumulative hazard functions for four groups in the sex-adjusted model were plotted to visualize the differences in the risk trajectories of migraine (Figure 4.4).

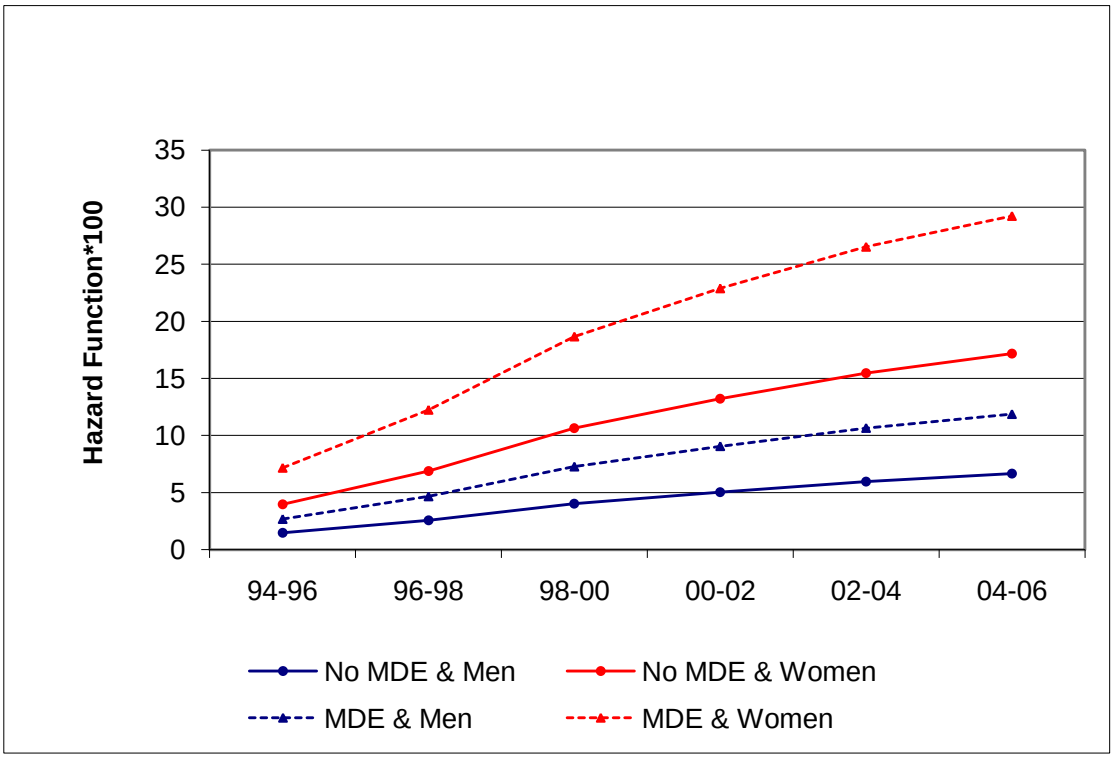

Figure 4.4 Cumulative hazard functions for migraine by MDE and sex

The hazard ratio and corresponding confidence intervals for the sex adjusted model, age adjusted, and stress adjusted models (Table 4.36) were lower than the unadjusted value thereby providing evidence of individual confounding by sex, age, and stress. The HR adjusted for childhood trauma was much lower and became non-significant (p-value = 0.19), indicating this variable acted as a strong confounder of the MDE and migraine risk relationship (Table 4.36). As these four key variables appeared to independently alter the MDE and migraine risk relationship, they were next combined stepwise in multivariate

models. The hazard ratio diminished slightly after adjustment for both sex and age (HR 1.4, CI 1.0-1.9) suggesting confounding (Table 4.37).

Table 4.37 Adjusted (sex and age) model for migraine risk

	HR (95% CI)
MDE(exposure)	*1.4 (1.0 - 1.9)**
Female sex	2.8 (2.4 - 3.3)
Age (0 = 46+, 1 = 12-25)	2.4 (2.0 - 3.0)
Age (0 = 46+, 1 = 26-45)	2.0 (1.6 - 2.4)

*p-value < 0.05

The association (HR 1.3, CI 1.0-1.8) between MDE and migraine risk was no longer significant (p-value = 0.065) with the addition of stress to the sex and age adjusted model (Table 4.38).

Table 4.38 Adjusted (sex, age and stress) model for migraine risk

	HR (95% CI)
MDE(exposure)	*1.3 (1.0 - 1.8)**
Female sex	2.8 (2.4 - 3.3)
Age (0 = 46+, 1 = 12-25)	2.0 (1.6 - 2.6)
Age (0 = 46+, 1 = 26-45)	1.9 (1.6 - 2.3)
Stress	1.5 (1.2 - 1.8)

*p-value = 0.065

Similarity, the addition of childhood trauma to the sex and age adjusted model (Table 4.39) made the association between MDE and migraine disappear. (Table 4.39)

Table 4.39 Adjusted (sex, age, and childhood trauma) model for migraine risk

	HR (95% CI)
MDE (exposure)	*1.0 (0.7 - 1.4)**
Female sex	2.7 (2.2 - 3.2)
Age (0 = 46+, 1 = 12-25)	2.4 (1.9 - 3.0)
Age (0 = 46+, 1 = 26-45)	2.0 (1.7 - 2.4)
Childhood trauma	1.3 (1.1 - 1.6)

*p-value = 1.0

As demonstrated in the previous models, the individual Wald tests for sex, age, stress, and childhood trauma remained significant in the expanded model (Table 4.40). However, the combination of these covariates in one model attenuated the association (HR 0.9, CI 0.7-1.2) between MDE and migraine further making it no longer evident.

Table 4.40 Adjusted (sex, age, stress, childhood trauma) model for migraine risk

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

*p-value = 0.6, **p-value < 0.05

Results from the multivariate proportional hazards models presented here (summarized in Table 4.41) show the association between MDE and migraine risk disappears with the inclusion of stress or childhood trauma.

Table 4.41 Model comparison for migraine risk

	HR (95% CI)	p-value
Unadjusted	*1.8 (1.3 - 2.4)*	*<0.001*
Adjusted, sex only	1.6 (1.2 - 2.1)	<0.005
Adjusted, sex & age	1.4 (1.0 - 1.9)	<0.05
Adjusted, sex, age & stress	1.3 (1.0 - 1.8)	0.07
Adjusted, sex, age & childhood trauma	1.0 (0.7 - 1.4)	1.0
Adjusted, sex, age, stress, childhood trauma	0.9 (0.6 - 1.2)	0.6

Chapter Five: Discussion

5.1 Introduction

The present study is one of the few to study the bidirectional association between migraine and MDE in a large representative community study. A number of conclusions can be drawn:

1. Migraine is associated with an increased incidence of MDE.
2. MDE is associated with an increased incidence of migraine.
3. Stress and childhood trauma may account for the association between MDE and migraine.

5.2 Summary of key findings

5.2.1 Migraine is associated with an increased incidence of MDE

The sex and age adjusted estimate of the association between migraine and incident MDE in the present study (HR 1.8,CI 1.5-2.2) is in the same direction as earlier studies (Breslau & Davis 1993; Breslau et al. 1994a). However, the magnitude of the association is weaker than previously reported. The association (HR 1.4, CI 1.2-1.8) between migraine and incident MDE persisted after adjustments for other variables.

Two other retrospective studies of the same cohort of young adults previously reported sex adjusted hazard ratios for migraine and incident MDE at 14 month and 3.5 year follow-up periods. The hazards ratios of these studies were 4.2 (CI 2.0-9.2) (Breslau & Davis 1993) and 3.4 (CI 2.4-4.8) (Breslau et al. 1994a) respectively. A third retrospective

cohort study reported an OR, adjusted for sex and comorbid psychiatric disorders, of 5.2 (CI 2.4-11.3) (Breslau et al. 2003), higher than the earlier study and the present study. Methodological differences may account for the variation in the estimates between these earlier studies and this study.

Samples drawn from HMOs rather than the general population may have more severe comorbid health conditions, in which case the association between migraine and incident MDE may appear stronger as a result of selection bias. This would occur if people with one of these conditions were more likely to be captured in the HMO population and they also had the other conditions, a plausible source of bias because comorbidity may influence health service use and therefore the probability of a diagnosis being made. Furthermore, the wide confidence intervals around the point estimates of the earlier studies indicate lack of precision due to small sample sizes. The estimates from the present study are more precise due the larger sample size. As such, whereas the point estimates from prior studies may differ considerably from those reported here; the prior studies may have overestimated the relative risk either as a result of chance or bias. Given these methodological differences, the present study does confirm the association between migraine and incident MDE seen in earlier retrospective cohorts and the hazard ratios may better reflect the magnitude of the association.

On the other hand, the measures of MDE and migraine in the current study were not as sophisticated as those used in the prior studies. If the NPHS included more

misclassification errors than the prior studies, the estimated effects may have been diluted. Non-differential misclassification bias may account for the lower hazard ratios reported here as compared to earlier studies.

5.2.2 MDE is associated with an increased incidence of migraine

The sex and age adjusted estimate of the association between MDE and incident migraine in the present study (HR 1.4 CI 1.0-1.9) is in the same direction as in earlier studies however, the magnitude of the association was weaker in this study. The unadjusted hazard ratio in the current study (HR1.8, CI 1.3-2.4) was attenuated by the inclusion of sex and age but the adjusted estimate continued to be statistically significant ($p<0.05$). The association disappeared entirely with additional adjustments.

Earlier studies have inconsistently reported an association between MDE and incident migraine. One study (Swartz et al. 2000) found no association between MDE and incident migraine. A longitudinal cohort study reported a sex, age and health care use adjusted hazards ratio of 2.1 (1.2-3.6) (Patten et al. 2008) only in respondents under 26 years of age. A retrospective cohort study of young adults reported a sex adjusted hazard ratio of 3.3 (CI 2.1-5.3) (Breslau et al. 1994b) for MDE and incident migraine. Another retrospective cohort study reported an OR adjusted for sex and comorbid psychiatric disorders of 3.0 (1.2-7.6) (Breslau et al. 2003) in adults aged 25 to 55 years.

Again, methodological differences or limitations may account for the variation in the estimates between these earlier studies and the present study. In some of the previous cohort studies (Breslau et al. 1994a; Breslau et al. 2003; Merikangas et al. 1990; Merikangas et al. 1993a; Patten et al. 2008) the samples were not representative of the general population and were notably younger or were made up of very restricted age groups, all of which may contribute to the differences in the magnitude of the observed association. However, the present findings confirm results from some earlier retrospective cohort studies reporting an association between MDE and incident migraine. Risk ratios from the earlier studies are stronger than in the present study (Breslau et al. 2003; Patten et al. 2008). However, the hazard ratios in this present study overlap with the lower bound confidence intervals from the earlier studies (Breslau et al. 2003; Patten et al. 2008). Either misclassification bias affecting the current estimates, or imprecision affecting the previous ones, or both, may account for the differences across all studies. However, the current study provides strong support for the idea that there is an increased risk of migraine in people with MDE. A key difference of this study is that the association observed here was found to disappear after adjustment for stressors and childhood traumas, and may arise due to confounding by these variables.

Previous studies (Breslau et al. 2003; Breslau et al. 1994b; Breslau et al. 2000) reported a significant bidirectional relationship between MDE and migraine. In the current study, the bidirectional association between MDE and migraine is weaker than in prior

studies. Nevertheless, persons with one condition are still at greater risk of developing the other condition and vice versa. Estimates from this study indicate that persons with migraine are 80% more likely to develop MDE than persons without migraine. Persons with MDE are 40% more likely to develop migraine compared to persons without MDE. An attractive explanation for such bidirectional effects is the possible existence of shared risk factors. Therefore, this bidirectional association observed in this population-based cohort study adds support to the suggestions of common neurobiology (Frediani & Villani 2007) or shared-etiology hypothesis (Breslau et al. 2003). Research about hypothesized shared etiologies has often focused on the serotonergic function and glutaminergic transmitter systems (Muller & Schwarz 2007; Pietrobon 2005; Stam et al. 2010) of the brain (Schur et al. 2009).

A recent Dutch genetic isolate study (Stam et al. 2010) attempted to determine whether the association between MDE and migraine was the result of heritable linkage (Ahn & Ashizawa 2010). This study concluded the heritability of migraine (particularly migraine with aura) could be due in part to a heritable component (Ahn & Ashizawa 2010) linked to major depression. The Dutch study provides additional evidence that the bidirectional relationship between MDE and migraine may be partly explained by shared underlying genetically determined disease mechanisms (Stam et al. 2010).

5.2.3 Stress and childhood trauma may account for the association between MDE and migraine

5.2.3.1 Stress

In this study, the inclusion of stress in the proportional hazards model attenuated the strength of the association between MDE and incident migraine making the association disappear completely. For example the age and sex adjusted HR for migraine risk was 1.4 (CI 1.0-1.9) but with the inclusion of stress diminished to 1.3 (CI 1.0-1.8). The disappearance of the association after adjustment for this variable may be due to the introduction of bias. A biased estimate could result from the statistical adjustment for a factor such as stress that is caused, in part, by the exposure (MDE) under study if this same factor, stress, is also associated with the outcome of migraine. A weakening of effect such as that observed in the current study may be due to the occurrence of a causal chain of events, or due to confounding. Confounding would imply that stress is associated with MDE and happens to be a risk factor for migraine. In this case, adjustment for the variable as a confounder would be justified. However, to the extent that MDE contributes to the experience of stress, adjustment would be inappropriate and would underestimate the impact of MDE. Another possibility is that exposure to stress leads both to an increased risk of MDE and migraine, in other words this variable may be a shared risk factor. More

detailed data would be required to fully isolate the temporal association between these variables.

5.2.3.2 Childhood trauma

In this study, the inclusion of childhood trauma attenuated the strength of the association between MDE and incident migraine making it no longer significant. For example, the age and sex adjusted HR for migraine risk was 1.4 (CI 1.0-1.9) but with the inclusion of stress diminished to 1.0 (CI 0.7-1.4). The disappearance of the association after the adjustment for childhood trauma may indicate this factor acts as a confounder. However, childhood trauma may be a shared determinant for both MDE and migraine. MDE may be a marker of neurobiologic changes secondary to childhood trauma that may also contribute to the etiology of migraine. Previous population-based studies have not addressed this issue. A recent Washington Twin study (Schur et al. 2009) about the shared genetic or environmental vulnerabilities underling migraine and major depression found a probable role of shared environmental factors in the etiology of major depression and/or migraine. The author noted that previous research (Tietjen et al. 2007) suggested that childhood maltreatment predisposed individuals to both major depression and migraine, hence, environmental factors may shape the expression of the bidirectional relationship. However, it is not possible to sharply distinguish between MDE in adulthood and the

occurrence of childhood and adult stressors, which are factors that may themselves be entwined with the etiology and pathophysiology of MDE.

Another possibility is that childhood trauma acts as a mediator between MDE and migraine risk. One criterion for defining mediation (Kraemer, 2007) stipulates a risk factor must precede the mediator. If using this criterion for determining mediation, childhood trauma is not likely mediating the association between MDE and migraine risk because childhood trauma would have occurred before MDE. However, this possibility cannot be completely ruled out because migraine can have an early age of onset, during childhood. Exploration of the underlying pathophysiological mechanisms should now be a greater priority rather than further statistical adjustment for such factors.

5.3 Potential impact of bias

Assessing if bias potentially impacted the findings is important to evaluate the validity of the study results. Hennnekens defines bias as "any systematic error in an epidemiologic study that results in an incorrect estimate of the association between exposure and the risk of disease" (Hennekens et al. 1987). This section identifies two possible sources of bias: selection bias and information bias, including speculation about the most likely direction and magnitude of their impact.

5.3.1 The effect of selection bias

Selection bias is a systematic error that may result from procedures used to select subjects or because there are subjects being lost from the original recruited sample prior to data analysis (Kleinbaum et al. 1982). In this study, selection bias would have resulted if the selection or inclusion of MDE (or migraineurs) and non-MDE (or non-migraineur) individuals was related to their development of migraine (or MDE). This is because of the fact that in a longitudinal study, subjects are selected based on exposure status, exposed or not exposed, and are followed until they develop disease i.e. everyone is free of depression, when depression is the outcome, at baseline so that migraine status as exposure could not have influenced the selection of depressed or non-depressed individuals. Whereas in case-control studies, selection bias is more likely to occur because the selection of cases and controls occurs at the same time as exposure assessment thus disease/non-disease selection can be easily influenced by the exposure status. In prospective cohort studies, the primary sources of selection bias are non-response or loss to follow up (Kleinbaum et al. 1982). In this case, selection bias will arise whenever the estimate of effect among the remaining exposed and unexposed participants is different from the true estimate of effect among exposed and unexposed groups in the original cohort (Kleinbaum et al. 1982). Since the best strategy for dealing with selection bias is to avoid it altogether, it helps to use high quality data collected by Statistics Canada. The NPHS employed state-of-the-art techniques

to maximize response, such as advance contacts, incentives, interviewer training to prevent refusals and reduce attrition, which included "Change of Address" card and obtaining information about alternative contacts. In the event that the respondent was not traced, the NPHS searched telephone directories and commercial CD-ROMs for their name, contact relatives with the same last name, etcetera, and also searched mortality registry files and institutions databases. In this analysis, attrition due to inability to trace respondents was 23%, 13.3% of respondents died, 7.0% did not provide information about MDE status and only 0.8% did not provide information about migraine status. A prior study about the NPHS data found attrition was related to several variables, but not to major depression or migraine (Swain et al. 1999). The loss to follow-up in this 12 year study was below the suggested proportion that are generally expected to raise serious questions about the study results (Hennekens et al. 1987). Overall, loss to follow-up over the course of the 12 year study period was relatively low and was not likely related to either MDE or migraine. Therefore, it is unlikely that selection bias was introduced due to loss to follow-up in this study.

5.3.2 The effect of information bias

Information or measurement bias can result "from systematic differences in the way data on the exposure or outcome are obtained from the various study groups" (Hennekens et al. 1987). Bias resulting from misclassification that does not necessarily differ in its

frequency between comparison groups is discussed in the subsequent section. Furthermore, recall bias "can lead to either an over- or underestimate of the association between exposure and disease, depending on whether the cases recall their exposure to a greater or lesser extent than the controls" (Hennekens et al. 1987). Interview bias refers to systematic differences in the collection of information (Hennekens et al. 1987). It is unlikely that either of these types of bias influenced this study. Questions about migraine and MDE status were based on past year observations, therefore, recall bias is expected to be small for this relatively short recall period. The NPHS employs rigorous training procedures and used computer-assisted questionnaires. The potential for interview bias is therefore limited. Interview bias could have occurred if respondents who were ill or had preconceived notions such as stigma concerning either migraine or MDE were more likely to give responses they believed to be desired by the interviewer. However, recall bias and interviewer bias are not the only sources of measurement bias.

5.3.3 The effect of misclassification bias

Misclassification bias is a form of information bias and occurs when "subjects are erroneously categorized with respect to either exposure or disease status" (Hennekens et al. 1987). Because non-differential misclassification "increases the similarity between the exposed and non-exposed groups, any true association between the exposure and disease will be diluted" (Hennekens et al. 1987). As Hennekens explains "Studies utilizing only

self-reported exposures may be subject to substantial amounts of misclassification, depending on the nature or the study population and the particular exposures" (Hennekens et al. 1987). This study relies on self-report for the assessment of both exposure and disease. Both the CIDI-SF and the self-report of migraine items may have been subject to error (e.g., the migraine rating is based on a health professional diagnosis, but professionals can make errors). In cohort studies such as this, the assessment of exposure status at baseline occurs at the time when disease status is unknown (i.e. everyone is free of disease initially and only they develop disease later) therefore any misclassification would likely be non-differential. For instance, as error in the assessment of MDE would probably not affect error in the assessment of migraine, the likely type of misclassification to result would be non-differential misclassification bias, potentially biasing the hazard ratios toward the null value.

5.3.3.1 Misclassification in migraine

The presence of migraine in this study was based on self-report of a diagnosis by a health professional, and not strictly diagnosed according to the IHS diagnostic criteria (Headache Classification Committee of the International Headache Society 1988). The degree to which the self-reported diagnosis of migraine were inaccurate because of reporting error is unknown, however, the estimates of prevalent migraine at each cycle (7.5% to 9.6%) in the NPHS are comparable to other cross-sectional Canadian studies

(Gilmour & Wilkins 2001; Jette et al. 2008; Molgat & Patten 2005). However, these studies all used similar methods and do not provide strong evidence that the measures are valid. It should be noted that these previous studies all used similar data sources that would have been vulnerable to similar types of measurement error. Some respondents suffering from chronic headaches might have been tallied as migraine sufferers and up to 50% (Cooke & Becker 2010; O'Brien et al. 1994) of respondents with migraine may not have been diagnosed by a health professional. It is possible in both of the scenarios that the misclassification of migraine could depend on MDE. If depressed respondents were more likely to report migraine diagnoses than non-depressed respondents, for example because of a tendency to somatise, this would inflate the hazards ratio. If this type of bias was present in this study the estimates (HRs) may overestimate the true association between migraine and MDE.

5.3.3.2 Misclassification in MDE

The NPHS used an abbreviated measure (CIDI-SF) for MDE as opposed to the detailed full version of the CIDI. It has been noted that unlike the full version of the CIDI, the CIDI-SF does not exclude depressive moods due to physical illness or bereavement and may therefore be vulnerable to false positives (Patten et al. 2000). The diagnostic accuracy of MDE is unlikely to differ depending on migraine status; the expected result is nondifferential misclassification bias. However, it is conceivable that some mechanisms

may have led to non-differential misclassification. For example, gastrointestinal side effects of analgesic medications such as opiates used by migraine sufferers may have contributed to the occurrence of false positive CIDI-SF ratings by affecting appetite items.

5.4 The effect of confounding

Confounding occurs when an observed association, or lack of one, is in due to mixing of effects between the exposure, the disease, and a third factor. This third factor, the confounder, must be associated with the exposure and independently affect the risk of developing the disease (Hennekens et al. 1987). In this study, the methods used to evaluate and control confounding included stratification and multivariate analysis. Age and sex were both indentified as potential confounders in the evaluation of both migraine and incident MDE and MDE and incident migraine, therefore, these variables were included in the proportional hazard models. In the stratified analysis, potential confounders were evaluated one at a time. At this stage, any variables that appeared to alter the observed estimate were identified. These variables were then included in the multivariate analysis. Similarly, potential cofounders were included in the subsequent models if alterations in the hazard ratio were observed after one at a time adjustments each potential confounders.

Confounding may also have systematically affected the final estimates if variables other than those available in the NPHS dataset were associated with both migraine and MDE. In particular, as the NPHS did not ask respondents about other psychiatric disorders

such as anxiety or stress reactivity. It is possible that the final estimates presented in this study may be residually confounded by the effect of other psychiatric conditions on incident migraine, however, it was not possible to examine this using the NPHS data.

5.5 The Potential role of chance

The role of chance may impact the "observed study results simply because of random variation from sample to sample" (Hennekens et al. 1987). Random error could have impacted this study due to the multiple comparisons done in the cross-sectional and longitudinal analysis. This type of random error, type I (alpha), would have resulted if an observed association between MDE and incident migraine, or vice versa, was deemed important when no association was actually present. A type I error can be defined as "an error in rejecting a true null hypothesis or declaring a difference exists when one does not" (Porta & International Epidemiological Association 2008). A second type of error, a type II (beta) error, could have occurred in this study if the study did not have enough power to detect an association if one existed. However, in this study type II error is likely minimal because the NPHS data was comprised of a large data set with ample sample size for detecting an association between migraine and MDE. In this regard, the estimation procedure was more precise than prior studies on the topic. In general, the relatively narrow confidence intervals in this study indicate a smaller amount of random error of the estimations.

5.6 Validity and generalizability

The evaluation of chance, bias, and confounding were explored as alternative explanations for the results in this study. These factors were unlikely to have had a major influence on the study results therefore the observed bidirectional association between migraine and MDE should be valid. As the internal validity of the study has been established, it is necessary to determine if the findings are generalizable to other populations. The NPHS target population consisted of household residents, limiting generalizability to Canadians who were homeless, institutionalized, or living on Indian reserves, Crown Lands, or on Canadian Forces bases.

5.7 Ethical considerations

The ethical considerations involved with this project were relatively minor. Statistics Canada employed strict usage rules for the NPHS data to ensure the anonymity of respondents. These rules include guidelines to govern the release and/or publication of estimates calculated from NPHS data. For this reason, the study could not harm participants. NPHS respondents provided informed consent to participate, voluntarily, in the data collection. In addition, ethical approval to conduct this research was obtained from the University of Calgary Conjoint Health Research Ethics Board.

5.8 Strengths and limitations of the Study

5.8.1 Strengths

A strength of this present study is that the measures of MDE and migraine were repeated at two year follow-up intervals and occurred over a longer period than previous studies on the topic. Second, the high participation rate and sampling procedures employed by Statistics Canada make the results representative of a large proportion of Canadians except for those previously mentioned as living in institutions, residents of first nations and those living in remote areas. Third, this study examined the reciprocal relationship between MDE and migraine using the same cohort of people in a longitudinal study. Furthermore, this study was longitudinal rather than cross-sectional in nature therefore it was possible to estimate the incidence of outcomes and establish a degree of temporality. Temporality is one of eight epidemiological criteria described by Bradford Hill (Hill 1965) that can provide evidence of a causal association between a factor and a disease (Porta & International Epidemiological Association 2008). The remaining Hill criteria for causality are consistency, strength, specificity, dose-response relationship, biological plausibility, coherence, experiment, and analogy. Results from this study are comparable (in direction, if not in the strength of association) to other studies about the longitudinal association between migraine and MDE. If another of Hill's criterion is applied, the evidence of an association between migraine and MDE risk, and MDE and migraine risk, in this Canadian

study are strengthened by prior studies across different populations in the Michigan, Zurich studies. As with all epidemiological studies, results from this analytic study are insufficient to conclusively establish causality, however, the estimates may provide powerful circumstantial evidence (Porta & International Epidemiological Association 2008) about the relationship between MDE and migraine. The current study provides substantial evidence that migraine contributes to the etiology of MDE, but does not provide strong causal evidence of an association in the other direction.

5.8.2 Limitations

Research has shown a stronger association between MDE and migraine with aura compared to migraine without aura (Breslau et al. 1994a; Breslau et al. 2003; Breslau et al. 2000). The NPHS was not able to distinguish between different migraine types therefore this issue was beyond the scope of this study.

The NPHS only collected information every two years. At each follow-up period, questions about MDE and migraine only pertained to the preceding year leaving a one year gap with no diagnostic information about MDE or migraine. A respondent may have become depressed (or been diagnosed with migraine) in the first year following an interview, but this information not available. These gaps in information may have diluted the strength of some of the relationships. Respondents with missing values for MDE (or migraine) at a cycle were considered to not have MDE (or migraine). If non-response for to

MDE or migraine questions were higher among individuals experiencing MDE or migraine, the results may be underestimated.

5.9 Areas for future study and implications

Future research should explore the mechanisms underlying the bidirectional association between MDE and migraine, whether they be health behaviours or psychosocial factors. The results from this study indicate that the elevated risk of migraine in people with MDE is related to childhood traumas and adult stressors such that the biological connections between these variables, stress-response systems and migraine, should be a focus of research. Future epidemiological studies in Canada should try to adopt the IHS criteria in order to differentiate between different migraine types and to examine the accuracy of migraine self-report in prior population-based studies.

Multiple epidemiological studies including the current study have reported similar results suggesting a causal relationship between migraine and MDE risk. In view of this association between migraine and MDE, the next step should focus on exploring how this information can be used by clinicians. In particular, there should be feasibility and effectiveness studies about: primary prevention of MDE in the migraine population by improving migraine management; early detection of MDE in migraine clinic settings by heightening awareness of the association between MDE and migraine, or through formal case-finding efforts; consideration of treating migraineurs with MDE with a single agent

that addresses both conditions to minimize side effects; and finally by ensuring access to mental health resources in settings where migraine is managed.

Although the epidemiology suggests a causal relationship between migraine and MDE risk, the same is not true about the association between MDE and migraine risk. Given the results from this study, it will be critical for future studies to include childhood trauma and stress as factors associated with MDE and migraine risk, especially to replicate and confirm the results reported. Evidence from biologically based studies are needed to clarify the mechanisms behind the association between MDE, migraine, stress, and childhood trauma. Future studies should consider inclusion of biological measures such as brain imaging and stress hormone levels. While the etiological connections between MDE and migraine risk needs further study, the results reported here confirm that the risk of migraine in those with MDE is elevated. Thus, clinicians and other health professionals should adopt strategies to deal with the comorbidity, such as case-finding, access to specialized care and parsimonious pharmacotherapy.

5.10 Conclusions

Findings from this study and previous research indicate the relationship between MDE and migraine is unlikely due to chance. Prior research describing a bidirectional association between MDE and migraine, suggests a common neurobiology (Frediani & Villani 2007). This study and previous research indicate that environmental factors such as

childhood trauma and stress may shape the expression of this bidirectional relationship, however, the precise mechanisms are not yet known. A bidirectional association between migraine and MDE could mean: (1) the association between migraine and depression is due to confounding by bio-psycho-social factors common to both conditions, as in shared vulnerability hypothesis or (2) the association may also be causally reciprocal, as in migraine as risk factor for MDE and vice versa, even after for adjustment for common vulnerability factors. Reciprocal causality could mean that treatment of one condition may prevent the onset of the other, yet if the shared-vulnerability hypothesis is true then this is not the case.

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APPENDIX A: International Headache Society - Diagnostic criteria for Migraine

In 1988, the International Headache Society published criteria for the diagnosis of a number of different headache types. Criteria for the more common headaches, namely migraine with and without aura are reproduced below. (Headache Classification Committee of the International Headache Society 1988)

Migraine without aura (MO) diagnostic criteria

A. At least five headache attacks lasting 4 - 72 hours (untreated or unsuccessfully treated), which has at least two of the four following characteristics:

1. Unilateral location
2. Pulsating quality
3. Moderate or severe intensity (inhibits or prohibits daily activities)
4. Aggravated by walking stairs or similar routine physical activity

B. During headache at least one of the two following symptoms occur:

1. Phonophobia and photophobia
2. Nausea and/or vomiting

Migraine with aura (MA) diagnostic criteria

A. At least two attacks fulfilling with at least three of the following:

1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem functions
2. At least one aura symptom develops gradually over more than four minutes, or two or more symptoms occur in succession
3. No aura symptom lasts more than 60 minutes; if more than one aura symptom is present, accepted duration is proportionally increased
4. Headache follows aura with free interval of at least 60 minutes (it may also simultaneously begin with the aura

B. At least one of the following aura features establishes a diagnosis of migraine with typical aura:

1. Homonymous visual disturbance
2. Unilateral paresthesias and/or numbness
3. Unilateral weakness
4. Aphasia or unclassifiable speech difficulty

APPENDIX B: Short-Form Composite International Diagnostic Interview (CIDI-SF) Questions from National Population Health Survey Questionnaire

The following description and questions were taken from the NPHS, Household Component, Cycle 7 (2006/2007) documentation and Questionnaire (Statistics Canada, 2008)

Depression Scale – Predicted Probability (MHCnDPP)
Based on MHC*n*DSF (Source: MHC*n*_2, MHC*n*_3, MHC*n*_4, MHC*n*_5, MHC*n*_6, MHC*n*_8A, MHC*n*_8B, MHC*n*_10, MHC*n*_11, MHC*n*_12, MHC*n*_13, MHC*n*_16, MHC*n*_17, MHC*n*_18, MHC*n*_19, MHC*n*_21A, MHC*n*_21B, MHC*n*_23, MHC*n*_24, MHC*n*_25 and MHC*n*_26).

This derived variable calculates the probability (expressed as a proportion) that the respondent would have been diagnosed as having experienced a major depressive episode in the past 12 months, if they had completed the *Long-Form Composite International Diagnostic Interview (*CIDI).

The predicted probability (MHC*n*DPP) was assigned based on respondents' short-form scores.

MH_Q02 *MHCB_2*
During the past 12 months, was there ever a time when you felt sad, blue, or depressed for two weeks or more in a row?
1 Yes
2 No (Go to MH_Q16)
DK, R (Go to next section)

MH_Q03 *MHCB_3*
For the next few questions, please think of the 2-week period during the past 12 months when these feelings were the worst.

During that time, how long did these feelings usually last?
INTERVIEWER: Read categories to respondent.
1 **All day long**
2 **Most of the day**
3 **About half of the day (**Go to MH_Q16)
4 **Less than half of a day (**Go to MH_Q16)
DK, R (Go to next section)

MH_Q04 *MHCB_4*
How often did you feel this way during those 2 weeks?
INTERVIEWER: Read categories to respondent.
1 **Every day**
2 **Almost every day**
3 **Less often (**Go to MH_Q16)
DK, R (Go to next section)

MH_Q05
During those 2 weeks did you lose interest in most things?

MHCB_5

1 Yes (KEY PHRASE = Losing interest)
2 No
DK, R (Go to next section)

MH_Q06 **Did you feel tired out or low on energy all of the time?**
MHCB_6

1 Yes (KEY PHRASE = Feeling tired)
2 No
DK, R (Go to next section)

MH_Q07 **Did you gain weight, lose weight or stay about the same?**
MHCB_7

1 Gained weight (KEY PHRASE = Gaining weight)
2 Lost weight (KEY PHRASE = Losing weight)
3 Stayed about the same (Go to MH_Q09)
4 Was on a diet (Go to MH_Q09)
DK, R (Go to next section)

MH_Q08A **About how much did you [gain/lose]?**
MHCB_8A INTERVIEWER: Enter amount only.
|_|_| Weight
(MIN: 1) (MAX: 99; warning after 20 pounds / 9 kilograms)
DK, R (Go to MH_Q09)

MH_Q08B INTERVIEWER: Was that in pounds or in kilograms?
MHCB_8B
MHCB_8LB 1 Pounds
MHCB_8KG 2 Kilograms
(DK, R are not allowed)

MH_Q09 **Did you have more trouble falling asleep than you usually do?**
MHCB_9

1 Yes (KEY PHRASE = Trouble falling asleep)
2 No (Go to MH_Q11)
DK, R (Go to next section)

MH_Q10 **How often did that happen?**
MHCB_10 INTERVIEWER: Read categories to respondent.
1 **Every night**
2 **Nearly every night**
3 **Less often**
DK, R (Go to next section)

MH_Q11 **Did you have a lot more trouble concentrating than usual?**
MHCB_11

1 Yes (KEY PHRASE = Trouble concentrating)
2 No
DK, R (Go to next section)

MH_Q12 *MHCB_12* **At these times, people sometimes feel down on themselves, no good or worthless. Did you feel this way?**
1 Yes (KEY PHRASE = Feeling down on yourself)
2 No
DK, R (Go to next section)

MH_Q13 *MHCB_13* **Did you think a lot about death - either your own, someone else's or death in general?**
1 Yes (KEY PHRASE =Thoughts about death)
2 No
DK, R (Go to next section)

MH_C14 If "Yes" in MH_Q05, MH_Q06, MH_Q09, MH_Q11, MH_Q12 or MH_Q13, or MH_Q07 is "gain" or "lose", go to MH_Q14C. Otherwise, go to next section.

MH_Q14C **Reviewing what you just told me, you had 2 weeks in a row during the past 12 months when you were sad, blue or depressed and also had some other things like (KEY PHRASES).**
INTERVIEWER: Press <Enter> to continue.

MH_Q14 *MHCB_14* **About how many weeks altogether did you feel this way during the past 12 months?**
|_|_| Weeks
(MIN: 2 MAX: 53)
(If > 51 weeks, go to next section.)
DK, R (Go to next section)

MH_Q15 *MHCB_15* **Think about the last time you felt this way for 2 weeks or more in a row. In what month was that?**

1 January
2 February
3 March
4 April
5 May
6 June
7 July
8 August
9 September
10 October
11 November
12 December

MH_Q16 **During the past 12 months, was there ever a time lasting 2 weeks or more**

MHCB_16 **when you lost interest in most things like hobbies, work or activities that usually give you pleasure?**

1 Yes
2 No (Go to next section)
DK, R (Go to next section)

MH_Q17 **For the next few questions, please think of the 2-week period during the past**
MHCB_17 **12 months when you had the most complete loss of interest in things.**

During that 2-week period, how long did the loss of interest usually last?
INTERVIEWER: Read categories to respondent.
1 **All day long**
2 **Most of the day**
3 **About half of the day (**Go to next section)
4 **Less than half of a day (**Go to next section)
DK, R (Go to next section)

MH_Q18 **How often did you feel this way during those 2 weeks?**
MHCB_18 INTERVIEWER: Read categories to respondent.
1 **Every day**
2 **Almost every day**
3 **Less often (**Go to next section)
DK, R (Go to next section)

MH_Q19 **During those 2 weeks did you feel tired out or low on energy all the time?**
MHCB_19
1 Yes (KEY PHRASE = Feeling tired)
2 No
DK, R (Go to next section)

MH_Q20 **Did you gain weight, lose weight, or stay about the same?**
MHCB_20
1 Gained weight (KEY PHRASE = Gaining weight)
2 Lost weight (KEY PHRASE = Losing weight)
3 Stayed about the same (Go to MH_Q22)
4 Was on a diet (Go to MH_Q22)
DK, R (Go to next section)

MH_Q21A **About how much did you [gain/lose]?**

MHCB_21A INTERVIEWER: Enter amount only.

|_|_| Weight
(MIN: 1) (MAX: 99; warning after 20 pounds / 9 kilograms)
DK, R (Go to MH_Q22)

MH_Q21B
MHCB_21B
MHCB_21L
MHCB_21K

INTERVIEWER: Was that in pounds or in kilograms?

1 Pounds
2 Kilograms
(DK, R are not allowed)

MH_Q22
MHCB_22

Did you have more trouble falling asleep than you usually do?

1 Yes (KEY PHRASE = Trouble falling asleep)
2 No (Go to MH_Q24)
DK, R (Go to next section)

MH_Q23
MHCB_23

How often did that happen?

INTERVIEWER: Read categories to respondent.

1 **Every night**
2 **Nearly every night**
3 **Less often**
DK, R (Go to next section)

MH_Q24
MHCB_24

Did you have a lot more trouble concentrating than usual?

1 Yes (KEY PHRASE = Trouble concentrating)
2 No
DK, R (Go to next section)

MH_Q25
MHCB_25

At these times, people sometimes feel down on themselves, no good, or worthless. Did you feel this way?

1 Yes (KEY PHRASE = Feeling down on yourself)
2 No
DK, R (Go to next section)

MH_Q26
MHCB_26

Did you think a lot about death - either your own, someone else's, or death in general?

1 Yes (KEY PHRASE =Thoughts about death)
2 No
DK, R (Go to next section)

MH_C27

If any "Yes" in MH_Q19, MH_Q22, MH_Q24, MH_Q25 or MH_Q26, or MH_Q20 is "gain" or "lose", go to MH_Q27C. Otherwise, go to next section.

MH_Q27C

Reviewing what you just told me, you had 2 weeks in a row during the past 12 months when you lost interest in most things and also had some other things like (KEY PHRASES).

INTERVIEWER: Press <Enter> to continue.

MH_Q27 **About how many weeks did you feel this way during the past 12 months?**
MHCB_27

|_|_| Weeks
(MIN: 2 MAX: 53)
(If > 51 weeks, go to next section.)
DK, R (Go to next section)

MH_Q28 **Think about the last time you had 2 weeks in a row when you felt this way. In**
MHCB_28 **what month was that?**

1 January
2 February
3 March
4 April
5 May
6 June
7 July
8 August
9 September
10 October
11 November
12 December

APPENDIX C: Diagnostic and Statistical Manual for Mental Disorders, 4th edition - Criteria for Major Depressive Episode

A) Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations

1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.

2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.

4) insomnia or hypersomnia nearly every day

5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

6) fatigue or loss of energy nearly every day

7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B) The symptoms do not meet criteria for a mixed episode.

C) The symptoms cause clinically significant distress or impairment in social, occupational,

or other important areas of functioning.

D) The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)

E) The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

(American Psychiatric Association 1994)