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Research paper

Major depressive episodes and mortality in the Canadian household population

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ABSTRACT

Objective: To explore the association between major depressive episodes (MDE) and subsequent mortality in a representative sample of the general household population, with adjustment for other determinants of mortality.
Method: The analysis used four datasets from the Canadian Community Health Survey (CCHS); the CCHS 1.1 (conducted in 2000 and 2001), the CCHS 1.2 (conducted in 2002), the CCHS 2.1 (conducted in 2003 and 2004) and the CCHS 3.1 (conducted in 2005 and 2006). Each survey included an assessment of past-year major depressive episodes (MDEs) and was linked to mortality data from the Canadian Mortality Database for January 1, 2000 to December 31, 2011. The hazard ratio (HR) for all-cause mortality was estimated in each survey sample. Random effects, individual-level meta-analysis was used to pool estimates from the four survey data sets. Estimates were adjusted for other determinants of mortality prior to pooling in order to help quantify the independent contribution of MDE to all-cause mortality.
Results: The unadjusted HR was 0.77 (95% CI 0.63–0.95). A naïve interpretation of this HR suggests a protective effect of MDE, but the estimate was found to be strongly confounded by age (age adjusted HR for MDE: 1.61, 95% CI 1. 34–1.93) and by sex (sex adjusted HR for MDE: 1.15, 95% CI 0.75–1.77). The age and sex adjusted HR was: 1.70 (95% CI 1.45–2.00). No evidence of effect modification by any determinant of mortality was found, including sex. After adjustment for a set of mortality risk factors, the pooled HR was weakened, but remained statistically significant, HR = 1.29 (I-squared = < 1%, tau-squared < 0.001, 95% CI 1.10–1.51). Smoking was the strongest single confounding variable.
Conclusions: MDE is associated with elevated mortality. The elevated risk is partially attributable to psychosocial, behavioral and health-related determinants. Since MDE itself may have caused changes to these variables, these estimates cannot fully quantify the independent contribution of MDE to mortality. However, these results suggest that clinical and public health efforts to counteract the effect of MDE on mortality may benefit from attention to a broad set of mortality risk factors e.g. smoking, physical activity, management of medical conditions.

Major depressive disorder is associated with increased all-cause mortality, but the strength of this association depends strongly on study design and covariate adjustments made in the individual studies. For example, an early review (Wulsin et al., 1999) noted that studies comparing patients hospitalized for depression to members of the general population (with adjustment for age and sex) have tended to find strongly elevated mortality ratios (on average 2.7) whereas studies of community samples have found weaker effects, in the range of 1.2–1.7. A more recent systematic review of unadjusted estimates arising from community studies reported a pooled relative risk of 1.81 (Cuijpers and Smit, 2002). However, this review identified considerable heterogeneity, suggesting that methodological characteristics of individual studies lead to variability in results. Moreover, some of the included studies used diagnostic instruments whereas others used symptom ratings. The various studies also examined different age ranges.

A Canadian study using data from a community-based prospective cohort called the National Population Health Survey found an age and sex adjusted HR of 2.0 (Patten et al., 2011), consistent with the Cuijpers and Smit estimate described above (Cuijpers and Smit, 2002). However, the association became weaker and was non-significant after adjustment for other potential determinants of mortality, including: age, sex, psychotropic medication use, marital status, income, employment, chronic medical conditions, smoking, alcohol consumption, pain,

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physical activity level, health-related activity restrictions and body mass index (HR = 1.1, 95% CI 0.7–1.7) (Patten et al., 2011). Notably, the width of the confidence intervals indicate that this estimate is consistent with wide range of population values, suggesting the need for larger studies with longer durations of follow-up. Another Canadian study (Gilman et al., 2017), examined data arising from three cohorts of survey participants linked to the national mortality database. In the most recent cohort, n = 1402 interviewed in 1992, an association of depression with mortality was seen (HR = 1.52 in men and HR = 1.51 in women). With adjustment for education, smoking, alcohol abuse and obesity the association weakened in men (HR = 1.32) but strengthened in women (HR = 1.62). This study also found effect modification by sex in one of the cohorts examined.

A better understanding of the association of major depression with mortality depends on overcoming inconsistencies and weaknesses of the prior literature. Ideally, studies should be based on representative samples, use a clinically relevant measure of major depression, have adequate sample size (and consequently precision), and have an ability to control for the effects of potential confounding variables. Recently, Statistics Canada has linked data from several large and detailed general health surveys (from 2000 to 2011) to data from the national mortality database from January 1, 2000 to December 31, 2011 (Sanmartin et al., 2016). These surveys included measures of MDE as well as many other determinants of health and mortality. The linked data file provides an opportunity to achieve greater precision and a more detailed description of the association of MDE with mortality in a representative sample.

1. Methods

1.1. Data source

In order to ensure an adequate number of deaths to support our analysis, we focused on linked data from four surveys: the CCHS 1.1 (2000/2001), CCHS 1.2 (2002), CCHS 2.1 (2003/2004) and the CCHS 3.1 (2005/2006). While more recent surveys have also been linked to mortality data by Statistics Canada (Sanmartin et al., 2016), only surveys conducted in 2005/2006, or before, were included in order to ensure an adequate number of deaths in the linked data deriving from each survey. This was important since a 2-step pooling procedure used to increase the precision of the HR estimates (described below) depends on an ability to estimate unadjusted and adjusted HRs in each of the data sets. The linkage was also limited to survey respondents who provided permission for linkage during their survey interview (approximately 90%) and whose data could be successfully linked to the mortality data, see Fig. 1. The linkage date was December 31, 2011. The dataset provided nearly 3 million person-years of observation.

A detailed description of data linkage procedures and its quality assessment has been reported elsewhere (Sanmartin et al., 2016). The linked data are available to researchers through the Canadian Research Data Centers Network. The current analysis took place in the Prairie Regional Data Centre on the University of Calgary Campus (Statistics Canada and the University of Calgary, 2018). The data linkage was approved by Statistics Canada's Executive Management Board and access to the data is governed by Statistics Canada's Directive on Record Linkage (Sanmartin et al., 2016). Under applicable ethical standards, this governance structure allows analyses to occur without ethics review board approval (Interagency Advisory Panel on Research Ethics, 2014).

1.2. Measures

Three of the surveys (CCHS 1.1, 2.1 and 3.1) assessed MDE using the Composite International Diagnostic Interview (CIDI) Short Form for Major Depression (Kessler et al., 1998b). This an abbreviated version of the University of Michigan modification of the CIDI section for MDE. The CIDI-SFMD screens respondents based on the answers to two items about depressed mood or anhedonia. If one or both of these symptoms occurred for at least two weeks, most of the day, nearly every day, a series of additional questions were asked. These cover other symptom-based criteria occurring during the same 2-week period (Kessler et al., 1998a). A scoring algorithm based on the original analysis suggested that a 90% probability of diagnosis of MDE (as defined by DSM-IIIR) in the past 12 months corresponds to reporting five of nine symptoms, at least one of which must be depressed mood or loss of interest, as defined above (Kessler et al., 1998a). This approximately corresponds to the symptoms of criterion A of the DSM-III-R, DSM-IV and DSM-5 (American Psychiatric Association, 2013). Some studies have assessed the validity of the CIDI-SFMD in comparison to other diagnostic tools. One study (Patten et al., 2000) reported that compared to the full WHO-CIDI, the CIDI-SFMD has a positive predictive value of 75%. Another study (Aalto-Setälä et al., 2002) reported that, compared to the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), the CIDI-SFMD has a sensitivity of 71%, and a specificity of 82%. Since this instrument addresses MDE only it is unable to distinguish bipolar from unipolar episodes. The CCHS 1.2 used a Canadian adaptation of the World Mental Health version of the CIDI (Kessler and Ustun, 2004). This interview included a module for mania, and can therefore differentiate between bipolar and unipolar MDEs. However, to be consistent with the other surveys included in this analysis, past-year MDE was used rather than Major Depressive Disorder.

Covariates included: age (treated as a continuous variable in most analyses), sex, marital status - dichotomized as married, including common-law, and an unmarried category that included both never married, previously married, widowed and divorced respondents. This decision was made because in Canada common-law and legally married spouses have very similar legal standing. Additional demographic covariates included: employment status (currently employed versus not), household income (assessed in quartiles and adjusted for family size and inflation), highest educational level achieved. Smoking status was also included in the analysis (daily and occasional smokers were compared to non-smokers, with the latter category including both never and former smokers), as was binge drinking (defined as 5+ drinks on any one occasion at least once per month in the past year). The surveys also assessed: self-reported professionally-diagnosed chronic conditions (self-reported, professionally diagnosed: arthritis, asthma, back problems, chronic lung disease, cataracts or glaucoma, cancer, Crohn's disease, diabetes, epilepsy, heart disease, high blood pressure, migraine, stroke, thyroid disease and peptic ulcer disease), a physical activity index and body mass index (based on self-reported height and weight). Fruit and vegetable consumption was assessed with a frequency-based measure. Items that asked about the usual daily consumption of fruit, green salad, potatoes, carrots and other vegetables. Fruit juices were not included in the frequency. The questionnaires recorded consumption as a count representing the number of times that fruits and vegetables were consumed in a “usual day.” In the analysis, the estimated average daily number of servings was included as a predictor of mortality. Physical activity was assessed using a list of recreational physical activities. The frequency of participation was multiplied by the duration of the activity and then by the metabolic intensity of the activity (as a multiple of the resting state). The final physical activity score was calculated as a sum of scores across all of a participant's activities to produce a total score expressed in kcal kg^{-1} day^{-1} and this was subsequently classified into inactive ($<$ 1.5 kcal kg^{-1} day^{-1}), moderately active (1.5–2.9 kcal kg^{-1} day^{-1}) and active ($\geq$3.0 kcal kg^{-1} day^{-1}) categories. Additional detail may be found in published sources, e.g. (Plotnikoff et al., 2004). Non-recreational physical activity was not assessed (e.g. strenuous physical work).

Not all of the covariates were assessed in all respondents in all of the survey iterations since Canadian provinces have the option to buy in (or not) to optional survey modules. Models containing any particular set of covariates therefore often included fewer subjects than the entire