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What characteristics are associated with earlier onset of first depressive episodes: A 16-year follow-up of a national population-based cohort

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ABSTRACT

This study examined characteristics associated with earlier onset of first depressive episodes. A nationally representative Canadian sample was randomly selected and followed from 1994 to 2011. At baseline complete data on depression history (Yes/No) and related diseases was available for *12,227* study subjects. Proportional hazard models were used. Meta-analyses were also applied to sync results across studies. Being younger, a woman, a Caucasian, a regular smoker, and having a chronic disease were significantly associated with the expedited trajectory for the onset of the first depressive episode. People were at the greater risk of having earlier onset of first depressive episodes at the 2-year follow-up ($p<0.001$), with the risk declining after four years ($p<0.001$). Women and men had different sets of characteristics associated with earlier onset of first depressive episodes. In meta-analyses, those having a chronic disease (HR_{pooled}= 1.31) and being a woman (HR_{pooled}= 1.43) were more likely to have earlier onset of first depressive episodes. This study provides solid evidence on the timing effect of these characteristics on first depressive episodes. Approaches focused on these identified risk characteristics should be prioritized to reduce the risk and postpone the onset of major depressive episode.

Keywords: Major depressive disorder; Characteristics; First-episode; Meta-analysis; Early onset

1. Introduction

The Global Burden of Disease 2012 systematic review of 291 diseases and injuries in 21 world regions from 1990 to 2010 concluded that major depressive disorder accounted for 2.5% of global DALYs, and its ranking increased from 15th to 11th (Murray et al., 2012). It has a profound impact on individuals and their families' quality of life, and also places a significant economic and social burden on society (Halfin, 2007).

From a preventive point of view there is a clear imperative for early detection or screening of major depressive disorder, identifying asymptomatic individuals at risk, and the application of effective treatments. The potential benefits such actions in altering the trajectory of disease is readily apparent. Early recognition and treatment of major depressive disorder can improve social function, increase productivity, and reduce absenteeism in the work places (Coulehan et al., 1997; Rost et al., 2004). Identifying those individuals at higher risk of earlier occurrence of first depressive episode is important, as prompt and appropriate interventions can then be applied to improve outcomes and quality of life.

Many epidemiological studies, mostly cross-sectional studies, have identified risk factors for major depression, including child abuse and adverse childhood experiences (Colman et al., 2009; Kessler et al., 2007; Li et al., 2016), low income (Salkever et al., 2014), unemployment (Pompili et al., 2014), smoking (He et al., 2014), physical inactivity (Meng and D'Arcy, 2013), unhealthy eating styles (Rawana et al., 2010), low social support (Theorell et al., 2015), stressful events, and neighbourhood deprivation (Mair et al., 2008).

Although few cohort studies have explored the risk profile of incident major depression among those having a comorbidity of another somatic or psychiatric disease (Aarts et al., 2009;

Peng et al., 2014; Pan et al., 2015), little is known about the relationship between risk factors and earlier onset of first depressive episode in prospective, population-based community samples. This study was designed to investigate characteristics associated with the earlier onset of first depressive episode in a large, population-based, prospective cohort study. In addition, meta-analyses were used to synthesize this present study's results on risk factors for earlier onset of first depressive episode with other published studies.

2. Methods

2.1 Data source and study design

Data analyzed was from the National Population Health Survey (NPHS), which is a population-based cohort study of a representative community sample of the Canadian population. The NPHS was designed to collect longitudinal information on population health from 1994/1995 to 2010/2011. Multistage stratification sampling was used to adjust geographic and socioeconomic characteristics and clustering. The NPHS longitudinal cohort initially included *17,726* participants in total. There was a 69.7% response rate for those who completed all nine cycles (Statistics Canada, 2012). The NPHS was approved by Statistics Canada ethics review process, and all respondents provided informed consent. More detailed information of this survey is described elsewhere (Tambay and Catlin, 1995; Swain et al., 1999).

2.2 Study sample

A total of *12,227* participants were selected for this study from the larger survey dataset. The eligibility criteria of the study sample selection was: 1) being aged 12 and more at the baseline

who had been followed-up to 2010/2011; 2) being depressed-free at the baseline, and had depression values (Yes/No) during the follow-ups; and, 3) not reporting any history of Alzheimer's disease or other dementias.

2.3 Outcome and predicators

The NPHS survey used an internationally recognized diagnostic questionnaire to assess the presence of a major depressive episode, the Composite International Diagnostic Interview Short Form (Kessler et al., 1998), to assess the presence of diagnostic symptoms in the past 12-months prior to the interview. A 90% predicative probability cut-off point had been validated against the revision of Diagnostic and Statistical Manual of Mental Disorders 3rd edition diagnostic criteria for major depressive episode. It was used to indicate the incidence of first depressive episode.

Characteristics examined in this study included *socio-demographic* factors (age, sex, race, marital status, income, education, and immigration status), *history of chronic disease*, and *lifestyle factors* (type of drinkers, level of physical activity, and type of smokers). The variable of "history of chronic disease" was dichotomous. Participants reporting any of the following long-term conditions that had been diagnosed by a health professional, were seen as having a history of chronic disease: arthritis or rheumatism, high blood pressure, asthma, chronic bronchitis, or other lung or breathing condition, diabetes, epilepsy, heart disease, angina, effects of a heart attack, effects of stroke, paralysis, incontinence, Alzheimer's disease or other dementias, osteoporosis or brittle bones, glaucoma, digestive conditions, kidney failure or disease, cerebral palsy, spina bifida, cystic fibrosis, multiple sclerosis, deformity, orthopaedic impairment or absence of arms, legs, hands or feet, cancer, or any other long-term condition. The variable of "type of drinker" was based on participant's drinking frequency, including regular drinker,

occasional drinker, former drinker, and abstainer. Physical activity was measured using criteria from Canadian Fitness and Lifestyle Research Institute that had been also used in other surveys, such as Ontario Health Survey (www.chass.utoronto.ca/ datalib/codebooks/utm/ohs/ohs90.htm), and the Campbell's Survey on Well-Being in Canada (www.cflri.ca/cflri/pa/surveys/88survey.html). Exposure to leisure time physical activity in the past three months prior to the interview was assessed through a series of questions, e.g. "Have you done any of following (physical activities) in the past three months?; "In the past three months, how many times did you participate in that activity?"; "How much time did you spend on each occasion?" Previously developed energy expenditure values were used to categorize an individuals' physical activity level, as active, moderate, and inactive (www.cflri.ca/cflri/pa/surveys/88survey.html). The variable of "type of smoker" was based on smoking frequency, which includes regular smoker (daily smoker), occasional smoker, former smoker, and non-smoker.

2.4 Statistical analyses

In order to examine the representativeness of the selected study sample, we compared the study sample to those not included in this study. Proportional hazard models were used to evaluate the relationship between characteristics and earlier onset of the first-episode of major depressive disorder. Schoenfeld residuals and –ln(-ln) survival plots were used to verify the proportional hazards assumption. In multivariate survival analyses, hazard ratios (HRs) were used to illustrate the relationship between characteristics and earlier onset of the first depressive episode. Interactions between factors were tested using Wald tests. The goodness of fit of the

final model was tested. To correct for the sample design effect, Statistics Canada recommended a bootstrap procedure that uses a set of 500 replicate sampling weights.

2.5 Meta-analyses

Meta-analysis was used to synthesize our findings with the results from other published cohorts indexed in the database of PubMed. Using PubMed with search terms 'depression' or 'depressive', and 'first' or 'new' or 'incident', and 'predicator', 'factor' or 'characteristic*', cohort studies of the association between risk factor and the first depressive episode were identified as of April, 2016. To be included in the meta-analyses, articles were evaluated for internal validity and following inclusion and exclusion criteria: 1) be published in English (before April 2016); 2) be a cohort study; 3) use clear diagnosis criteria for major depressive episode; and, 4) provide statistical indicators or original data to estimate the relationship between characteristics and major depressive episode. Meta-analyses were restricted to characteristics that were selected in this present study and consistently categorized across studies. Studies were excluded if characteristics studied were not found in this present study.

HRs for the contrast between the risk level and reference level of each selected factor were pooled using random-effects models. The inverse of the variance of the log HR was used to weight each HR from each study to calculate the pooled HR and its 95% confidence interval (CI). Heterogeneity between studies was tested by DerSimonian and Laird I^2 *statistic*, which is the proportion of variation in HRs attributable to heterogeneity (Schoenfeld and Loftus, 2005). Funnel plots and Egger's tests were used to check publication bias (Egger et al., 1997). Sensitivity analysis assessed the influence of each study on overall estimates by recalculating HR with each study being removed one at a time, and by only including those studies with large

sample size (N>=*1000*). Stata v.12, statistical software (StataCorp., USA) was used for all analyses.

3. Results

3.1 Characteristics of the study sample

A total of *12,227* participants of NPHS were selected for this study. The study sample was 12 years and more and depression-free at the baseline, and followed up for a 16-year period from 1994/95 to 2010/11. Additionally, there was complete data on major depressive episode during the period. Compared to non-selected survey subjects, the study sample had a higher proportion of older population, women, Caucasians, people living married or in a common-law relationships, people with higher income and better education, immigrants, regular drinkers and smokers, less active people, and people suffering with chronic diseases (data not shown). There were fewer men than women (48.2% vs. 51.8%). Men were more likely to be younger, in a relationship (married or common-law), with higher income and more education, regular drinkers and smokers, more active, and with less chronic disease ($p<0.05$).

3.2 Characteristics associated with having an earlier onset of the first episode of major depressive disorder during the 16-year follow-up

Proportional hazard models were used to evaluate the relationships between characteristics and having an earlier onset of the first depressive episode during the 16-year period, from 1994/95 to 2010/11. Table 1 shows the univariate and multivariate proportional hazard models for selected socio-demographic and health related characteristics in the study sample. Factors including the time of follow-up, age, sex, ethnicity, life style factors (smoking and drinking

habits), and whether or not having a chronic disease, each was independently associated with having an earlier onset of the first depressive episode. Variables with *p*-values less than 0.20 in the univariate analyses were forwarded into the initial multivariate proportional hazard model. After model fitting and proportional assumption test, younger people (≤45 years old), women, Caucasians, regular smokers, and people having a chronic disease were at the higher risk of having an earlier onset of the first depressive episode. In addition, the length of follow-up was also associated with having an earlier onset of the first depressive episode. Notably, people tend to have the first depressive episode within the 2-year follow-up (HR 1.13, 95% CI 1.10-1.15, $p<0.001$), but the risk of developing the first depressive episode was declined after the 4-year follow-up ($p<0.001$).

3.3 Characteristics associated with earlier onset of the first depressive episode for men and women

All analyses were done for women and men separately in order to compare those unique characteristics associated with earlier onset of the first depressive episode for different gender. For women, those who were younger (≤25 years old), being a Caucasian, being a regular smoker, and having a chronic disease, were more likely to report an earlier onset of first depressive episode ($p<0.05$). Again, after 4-year follow-up, their risk of having the first depressive episode decreased ($p<0.05$). In contrast, men who were aged less and/ or equal than 65 years, occasional drinkers, former drinkers, or abstainers, regular smokers, and having a chronic disease were at a greater risk of having an earlier onset of the first depressive episode ($p<0.05$). Among men, the risk of developing the first depressive episode decreased after 6-year follow-up ($p<0.05$).

3.4 Meta-analyses

A systematic search in the PubMed revealed only two characteristics (being a woman and having a chronic disease) found to be associated with earlier onset of the first depressive episode in this present study, were consistently found in other studies. Figure 1 and 2 present forest plots and pooled results for relationships between these two characteristics and earlier onset of the first depressive episode. The pooled HR of whether or not having a chronic disease linked to an earlier onset of the first depressive episode was based on 12 studies (N=*262,742*). The pooled $HR_{\text{chronic disease}}$ was 1.31 (95% CI 1.21-1.43), indicating that those who suffered a chronic disease were 1.31 times more likely to have an earlier onset of the first depressive episode compared to those who did not have a chronic disease. There was no evidence of publication bias (Egger's test t=1.66, p=0.13). The funnel plot of all the 12 studies did not show asymmetry. An influential analysis was conducted to assess the influence of each study on overall estimates by omitting one study at a time. The combined HR was 1.31 (95% CI 1.21-1.43), suggesting that having a chronic disease accelerated an earlier onset of first depressive episode.

The pooled HR of being a woman was based on *83,630* individuals from four cohorts. The pooled HR for women was 1.43 (95% CI 1.22-1.68), indicating that women were 1.43 times more likely to have an earlier onset of first depressive episode compared to men. There was no evidence of publication bias (Egger's test t=-0.06, p=0.96). The funnel plot of all four cohorts did not show asymmetry. The combined HR of the influential analysis was 1.43 (95% CI 1.22-1.68), clearly supporting that women had a greater risk of having an earlier onset of first depressive episode.

4. Discussion

In this national prospective, population-based, cohort study, being younger (≤45 years old), a woman, Caucasian, regular smoker, and having a chronic disease were significantly associated with increasing risk of developing an earlier onset of the first depressive episode. People were at the greater risk of having an earlier onset of the first depressive episode at the 2-year follow-up (HR 1.13, 95% CI 1.10-1.15, $p<0.001$). The risk was declining after the 4-year follow-up ($p<0.001$). Women and men had different sets of characteristics associated with developing earlier onsets of first depressive episodes. In meta-analyses, those having a chronic disease were 1.31 times more likely to develop an earlier onset of the first depressive episode. Compared to men, women were 1.43 times more likely to develop an earlier onset of the first depressive episode.

In agreement with previous literature, factors including being a woman, being a Caucasian, a regular smoker, and having a chronic disease were associated with first depressive episodes (Hung et al., 2013; Pedrelli et al., 2016; Ryu et al., 2016; Fluharty et al., 2017). Women are consistently found to be more frequently depressed than men across cultures. Derry in his recent review discussed the role of inflammation in major depressive disorder, and suggested that inflammation may be the reason for women's susceptibility to the disease as women are prone to be affected by several factors that elevate inflammation (Derry et al., 2015). Two hypotheses may explain the lower rate of first depressive episode among immigrations in this national sample: healthy immigrants effect (Meng and D'Arcy, 2012) and a slower process acculturation process for losing protection from their original cultures (Smith et al., 2007).

Studies have consistently reported the positive association between regular smoking and major depressive disorder. However, the literature remains unclear regarding the direction of this

association. In a recent systematic review, Fluharty and colleagues (2017) concluded that the literature on the prospective relationship between regular smoking and major depressive disorder was inconsistent in terms of the direction of association most strongly supported, and suggested future studies should employ methods for stronger casual inference to be made. It is not uncommon to see the association between major depressive disorder and other chronic mental and physical health problems. Ryu and colleagues (2016) used quantitative methods to identify the most influential contribution of chronic health problems to major depressive disorder in adults, and found among 24 chronic conditions, the most influential one was diabetes for those aged less than 60 years and rheumatoid arthritis or osteoarthritis for those over 60 years.

Notably, what this study particularly adds into the literature is the timing effect of these characteristics in developing an earlier onset of first depressive episode in a national community sample. In other words, these characteristics were more closely related to the accelerated occurrence of the first depressive episode. These characteristics not only indicate a higher risk for developing the disease, but also suggest an expedited trajectory of disease onsets. People with these characteristics are at the greater risk of developing the disease, and experience their first episodes at an earlier age. Given the importance of the first episode in the disease management and prevention of major depressive disorder, it is crucial to pay additional attention to these characteristics among people at the higher risk of the disease.

Although previous comorbidity studies have explored how these factors may contribute to the first depressive episode, with the emphasis of understanding how other comorbid health problems contribute to first depressive episode among people with a comorbidity of somatic or other mental health problems (Aarts et al., 2009; Hung et al., 2013; Kulkantrakorn and Jirapramukpitak, 2007; Luijendijk et al., 2010), the present study investigated how these factors,

as primary characteristics, contributed to the expedited development of first depressive episode in a national representative community sample. Our meta-analyses results further concluded the risk of having a comorbidity of other health problems and female gender could significantly accelerate the process of developing first depressive episode.

Major depressive disorder is significantly under-detected and under-treated (Judd et al., 1996). Early detection, and effective treatment can promote remission, prevent relapse, and reduce both emotional and financial burden of the diseases (Halfin, 2007). Like other chronic diseases, major depressive disorder has a very complex causal network, and many risk factors contribute the disease course. Clinicians should pay very close attention to these determinants associated with earlier onsets of the first depressive episode, in order to early and effectively detect those at a high risk of major depression.

The prospective study design, national representative community sample, and highly complete follow-up of the NPHS make information and selection bias less likely to occur. In addition, we used evidence-based approaches to synthesize the effect size of characteristics in developing an earlier onset of the first depressive episode. This study has several limitations. Firstly, although data used in this study included a wide range of characteristics, there is still a lack of information on diagnosis of psychiatric diseases (except major depressive episode), which may influence the relationships between characteristics and first depressive episode. Secondly, although many potential confounders were accounted for, the possibility of unknown or residual confounders remains. Thirdly, this study found statistically significant differences of several sample characteristics between selected and un-selected population. This will reduce the generalizability of the study findings. Fourthly, in the meta-analyses, the comparisons were made between those with and without another chronic disease. Because a small number of studies with

the data on comorbidity in general were identified, it restricted analyses by different health problems.

5. Conclusion

This study provides solid evidence on the timing effect of studied characteristics on the first depressive episode in a large-scale national longitudinal cohort. Given the limited resources available, and in order to achieve a better prevention payoff, attention should be given to effective and economic approaches focused on the identified characteristics to reduce the risk and postpone the occurrence of major depressive episode,.

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Disclosure of interest

The author reports no conflicts of interest with this study.

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Table 1
Proportional hazard models of characteristics associated with earlier onset of the first depressive episode for the study cohort

Characteristics	Primary Model HR, 95% CI	*P*-value	Final Model HR, 95% CI	*P*-value
Study follow-up				
Baseline	1			
2-year follow-up	1.142, (1.107-1.178)	<0.001	1.126, (1.103-1.151)	<0.001
4-year follow-up	1.025, (0.969-1.084)	0.390	1.015, (0.967-1.064)	0.547
6-year follow-up	0.906, (0.842-0.976)	0.009	0.894, (0.836-0.958)	0.001
8-year follow-up	0.781, (0.710-0.860)	<0.001	0.757, (0.693-0.828)	<0.001
10-year follow-up	0.632, (0.562-0.710)	<0.001	0.620, (0.556-0.691)	<0.001
12-year follow-up	0.432, (0.368-0.507)	<0.001	0.408, (0.348-0.479)	<0.001
14-year follow-up	0.315, (0.255-0.389)	<0.001	0.297, (0.241-0.366)	<0.001
16-year follow-up	0.140, (0.097-0.201)	<0.001	0.142, (0.100-0.201)	<0.001
Age				
12-18	1		1	
19-25	0.813, (0.577-1.144)	0.234	0.886, (0.649-1.210)	0.445
26-45	0.687, (0.471-1.000)	0.050	0.750, (0.531-1.060)	0.103
46-65	0.492, (0.333-0.727)	<0.001	0.526, (0.368-0.754)	<0.001
66+	0.189, (0.122-0.294)	<0.001	0.205, (0.133-0.313)	<0.001
Sex				
Men	1		1	
Women	1.726, (1.482-2.010)	<0.001	1.788, (1.547-2.067)	<0.001
Ethnicity				
Caucasians	1		1	
Others	0.703, (0.494-0.999)	0.049	0.719, (0.532-0.971)	0.032
Marital status				
Married/Common law	1			
Single	0.973, (0.842-1.124)	0.708		
Widowed/separated/divorced	1.046, (0.905-1.209)	0.539		
Income				
Not Poor	1			
Poor	1.063, (0.945-1.196)	0.305		
Education				
Secondary	1			
Some post-secondary	0.935, (0.791-1.104)	0.424		
Post-secondary	0.933, (0.736-1.184)	0.569		
Less than secondary	0.846, (0.673-1.062)	0.149		
Immigrant status				
Canadian born	1			
Immigrant	0.972, (0.740-1.278)	0.841		
Type of drinker				
Occasional/former/ abstainer	1			
Regular	0.880, (0.778-0.995)	0.041		

Type of smoker				
Never/former/occasional	1		1	
Regular	1.353, (1.155-1.584)	<0.001	1.331, (1.145-1.549)	<0.001
Chronic disease				
Without	1		1	
With	1.589, (1.415-1.784)	<0.001	1.636, (1.464-1.829)	<0.001
Physical activity				
Active	1			
Moderately active	0.968, (0.852-1.099)	0.611		
Inactive	1.013, (0.875-1.172)	0.867		

HR=Hazard ratio; CI=Confidence interval

Table 2
Proportional hazard models of characteristics associated with earlier onset of the first depressive episode for the study cohort (Women)

Characteristics	Primary Model HR, 95% CI	*P*-value	Final Model HR, 95% CI	*P*-value
Study follow-up				
Baseline	1		1	
2-year follow-up	1.162, (1.113-1.214)	<0.001	1.138, (1.104-1.173)	<0.001
4-year follow-up	1.069, (0.997-1.147)	0.061	1.032, (0.971-1.096)	0.315
6-year follow-up	0.929, (0.848-1.017)	0.111	0.886, (0.814-0.963)	0.005
8-year follow-up	0.850, (0.759-0.953)	0.005	0.782, (0.701-0.873)	<0.001
10-year follow-up	0.665, (0.572-0.773)	<0.001	0.643, (0.558-0.740)	<0.001
12-year follow-up	0.474, (0.391-0.575)	<0.001	0.432, (0.358-0.521)	<0.001
14-year follow-up	0.353, (0.274-0.455)	<0.001	0.322, (0.253-0.410)	<0.001
16-year follow-up	0.134, (0.088-0.205)	<0.001	0.139, (0.093-0.207)	<0.001
Age				
12-18	1		1	
19-25	0.617, (0.417-0.913)	0.016	0.699, (0.479-1.020)	0.063
26-45	0.492, (0.314-0.772)	0.002	0.551, (0.359-0.847)	0.007
46-65	0.378, (0.235-0.607)	<0.001	0.415, (0.264-0.653)	<0.001
66+	0.129, (0.077-0.215)	<0.001	0.147, (0.089-0.243)	<0.001
Ethnicity				
Caucasians	1		1	
Others	0.531, (0.313-0.901)	0.019	0.577, (0.363-0.917)	0.020
Marital status				
Married/Common law	1			
Single	0.971, (0.817-1.153)	0.736		
Widowed/separated/divorced	1.006, (0.847-1.194)	0.949		
Income				
Not Poor	1			
Poor	1.126, (0.989-1.282)	0.072		
Education				
Secondary	1			
Some post-secondary	0.912, (0.753-1.104)	0.344		
Post-secondary	0.894, (0.683-1.170)	0.415		
Less than secondary	0.819, (0.647-1.037)	0.097		
Immigrant status				
Canadian born	1			
Immigrant	1.085, (0.764-1.542)	0.648		
Type of drinker				
Occasional/former/ abstainer	1			
Regular	0.916, (00.796-1.054)	0.221		
Type of smoker				
Never/former/occasional	1		1	
Regular	1.250, (1.037-1.506)	0.019	1.223, (1.020-1.468)	0.030

Chronic disease				
Without	1		1	
With	1.526, (1.320-1.763)	<0.001	1.576, (1.368-1.817)	<0.001
Physical activity				
Active	1			
Moderately active	1.007, (0.852-1.161)	0.932		
Inactive	1.059, (0.878-1.275)	0.552		

HR=Hazard ratio; CI=Confidence interval

Table 3
Proportional hazard models of characteristics associated with earlier onset of the first depressive episode for the study cohort (Men)

Characteristics	Primary Model HR, 95% CI	*P*-value	Final Model HR, 95% CI	*P*-value
Study follow-up				
Baseline	1		1	
2-year follow-up	1.104, (1.058-1.152)	<0.001	1.124, (1.076-1.174)	<0.001
4-year follow-up	0.949, (0.866-1.040)	0.265	1.018, (0.932-1.113)	0.690
6-year follow-up	0.858, (0.752-0.979)	0.023	0.956, (0.844-1.084)	0.484
8-year follow-up	0.663, (0.555-0.793)	<0.001	0.771, (0.646-0.921)	0.004
10-year follow-up	0.576, (0.465-0.714)	<0.001	0.605, (0.497-0.737)	<0.001
12-year follow-up	0.360, (0.268-0.484)	<0.001	0.386, (0.289-0.515)	<0.001
14-year follow-up	0.253, (0.172-0.371)	<0.001	0.266, (0.180-0.394)	<0.001
16-year follow-up	0.149, (0.075-0.292)	<0.001	0.160, (0.081-0.313)	<0.001
Age				
12-18	1		1	
19-25	1.368, (0.769-2.433)	0.285	1.051, (0.593-1.863)	0.864
26-45	1.282, (0.680-2.419)	0.442	0.906, (0.440-1.866)	0.789
46-65	0.815, (0.414-1.605)	0. 553	0.552, (0.268-1.137)	0.107
66+	0.398, (0.178-0.891)	0.025	0.256, (0.112-0.585)	0.001
Ethnicity				
Caucasians	1			
Others	1.090, (0.637-1.868)	0.752		
Marital status				
Married/Common law	1			
Single	0.972, (0.742-1.274)	0.838		
Widowed/separated/divorced	1.141, (0.883-1.474)	0.312		
Income				
Not Poor	1			
Poor	0.970, (0.780-1.207)	0.786		
Education				
Secondary	1			
Some post-secondary	0.968, (0.733-1.278)	0.819		
Post-secondary	1.006, (0.682-1.485)	0.974		
Less than secondary	0.887, (0.565-1.391)	0.601		
Immigrant status				
Canadian born	1			
Immigrant	0.775, (0.528-1.138)	0.193		
Type of drinker				
Occasional/former/ abstainer	1		1	
Regular	0.794, (0.635-0.992)	0.042	0.794, (0.641-0.983)	0.035
Type of smoker				
Never/former/occasional	1		1	
Regular	1.539, (1.179-2.008)	0.002	1.514, (1.174-1.952)	0.001

Chronic disease				
Without	1		1	
With	1.699, (1.409-2.048)	<0.001	1.659, (1.376-2.000)	<0.001
Physical activity				
Active	1			
Moderately active	0.905, (0.753-1.087)	0.283		
Inactive	0.946, (0.759-1.178)	0.619		

HR=Hazard ratio; CI=Confidence interval

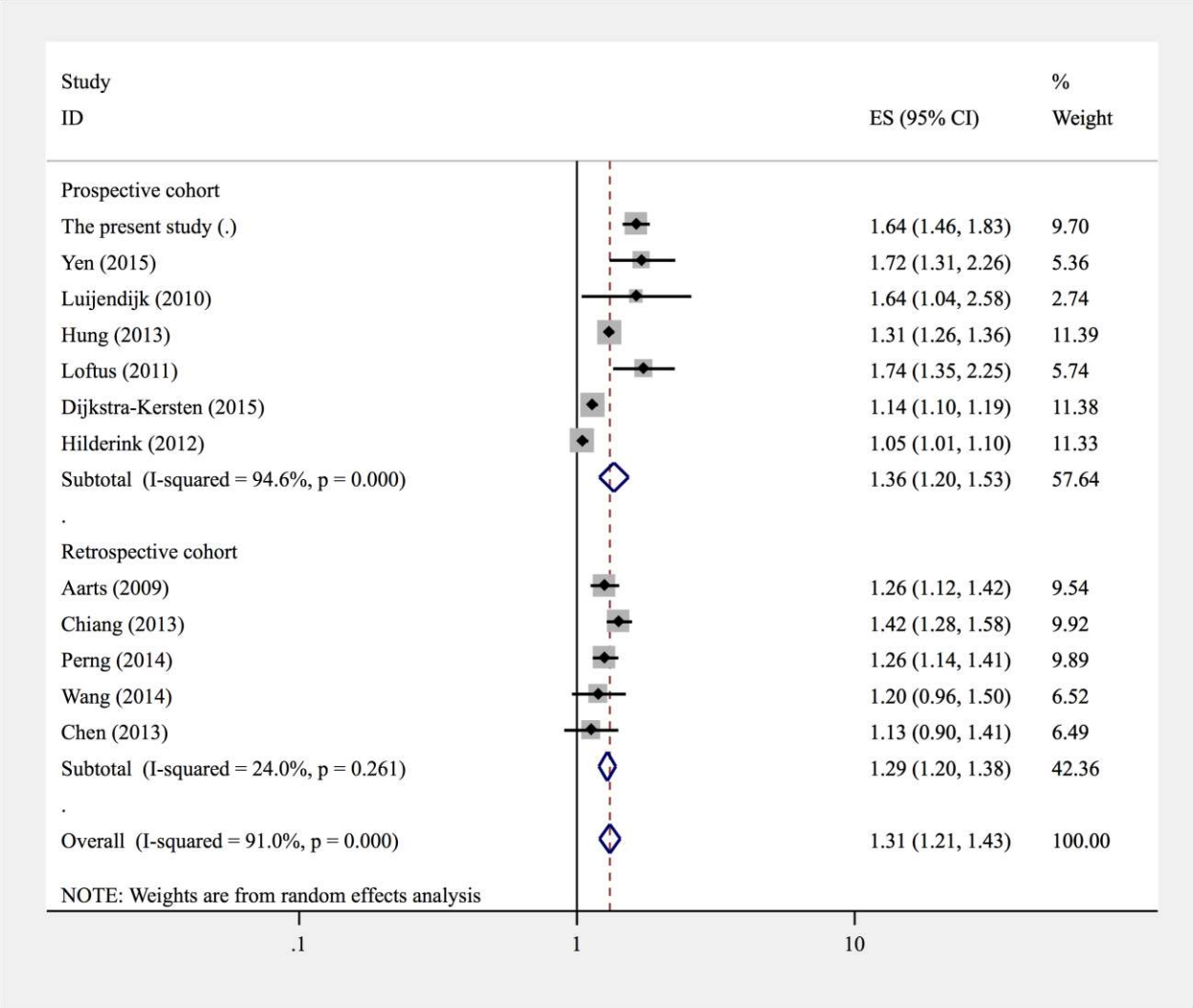

Figure 1
Forest plots of HRs and 95% CIs comparing having a chronic disease vs. without having a chronic disease for the first depressive episode, from random-effects meta-analyses. Separate plots are for prospective and retrospective cohort studies. Studies were weighted according to the inverse of the variance of the log hazard ratio estimate. Diamonds represent the pooled HR estimates and 95% confidence interval for each category.

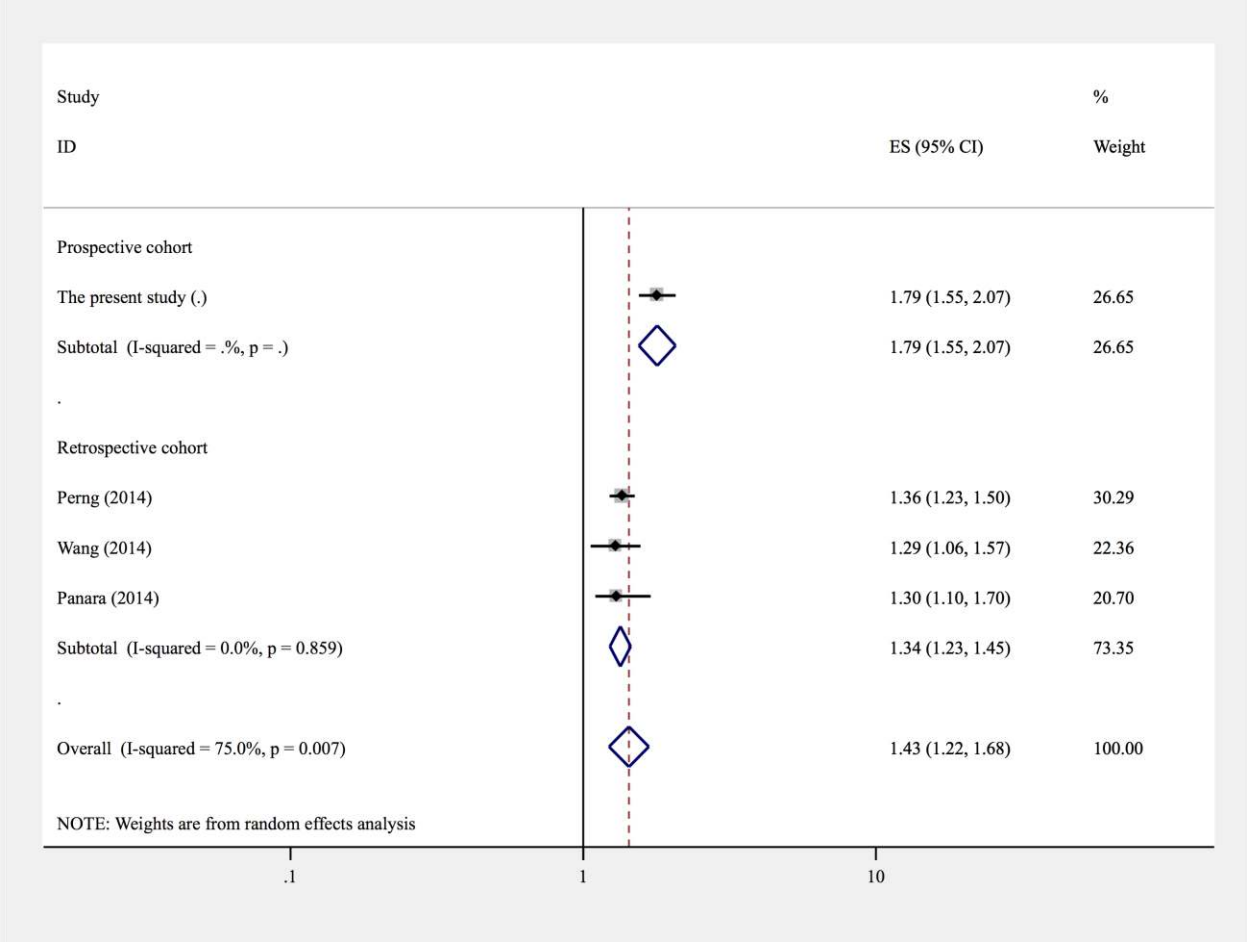

Figure 2
Forest plots of HRs and 95% CIs comparing women vs. men for the first depressive episode, from random-effects meta-analyses. Separate plots are for prospective and retrospective cohort studies. Studies were weighted according to the inverse of the variance of the log hazard ratio estimate. Diamonds represent the pooled HR estimates and 95% confidence interval for each category.