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Does Depression Predict Coronary Heart Disease and Cerebrovascular Disease Equally Well? The HeSSup Prospective Cohort Study

Running Head: Depression, Coronary heart and cerebrovascular diseases

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ABSTRACT

Background: The relationship between depression and cerebrovascular disease (CBVD) continues to be debated although little research has compared the predictive power of depression for coronary heart disease (CHD) to that for CBVD within the same population. This study aimed to compare the importance of depression for CHD and CBVD within the same population of adults free of apparent cardiovascular disease**.**

Methods: A random sample of 23282 adults (9507 men, 13775 women) aged 20-54 years were followed-up for 7 years. Fatal and first non-fatal CHD and CBVD events were documented by linkage to the National-hospital-discharge and mortality registers.

Results: Sex-age-education-adjusted Hazard Ratio (HR) for CHD was 1.66 (95% confidence interval (CI) 1.24-2.24) for participants with mild to severe depressive symptoms, i.e. those scoring 10 or more on the 21-item Beck-Depression-Inventory, and 2.04 (1.27-3.27) for those who filled antidepressant prescriptions compared to those without depression markers in 1998, i.e., at study baseline. For CBVD, the corresponding HRs were 1.01 (0.67-1.53) and 1.77 (0.95-3.29). After adjustment for behavioural and biological risk factors these associations were reduced but remained evident for CHD, the adjusted HRs being 1.47 (1.08-1.99) and 1.72 (1.06-2.77). For CBVD, the corresponding multivariable adjusted HRs were 0.87 (0.57-1.32) and 1.52 (0.81-2.84).

Conclusions: Self-reported depression using a standardized questionnaire and clinical markers of mild to severe depression were associated with an increased risk for CHD. There was no clear evidence that depression is a risk factor for CBVD, but this needs further confirmation.

Keywords: depression, coronary heart disease, cerebrovascular disease

KEY MESSAGES

_ The relationship between depression and cerebrovascular disease (CBVD) continues to be debated although little research has compared the predictive power of depression for coronary heart disease (CHD) to that for CBVD within the same population.

_ After adjustment for basic socio-demographic factors and biobehavioural risk factors, participants with mild to severe depressive symptoms, i.e. those scoring 10 or more on the 21-item Beck-Depression-Inventory, and those who filled antidepressant prescriptions had an increased risk for CHD over the 7 years of follow-up compared to those without depression markers

_ There was no clear evidence that depression is a risk factor for CBVD, but this needs further confirmation.

INTRODUCTION

Cardiovascular disease, including coronary heart disease (CHD) and cerebrovascular disease (CBVD), is the leading cause of death, major morbidity, and disability in the world.(1) Approximately 17.5 million people died from cardiovascular diseases in 2005, representing 30% of all deaths globally.

Research has identified cigarette smoking, high alcohol intake, high cholesterol levels, obesity, hypertension, diabetes, unhealthy diet and physical inactivity as important risk factors for cardiovascular disease (2). Findings from prospective studies using rigorous methods show that depression may also be a risk factor in the pathophysiological progression of cardiovascular disease (3). Several recent studies provide compelling evidence showing depression to influence the onset and outcome of CHD, indicating that it may act as a distal risk factor and play a role in disease prognosis (4). Successive meta-analyses show depression to increase the risk for onset of CHD, with pooled relative risks between 1.6 and 1.8 (5-7).

While there appears to be a consensus on the depression-CHD link, more controversies remain regarding the association between depression and CBVD. In fact, fewer studies have examined the association between depression and the risk for the onset of CBVD, and the findings are inconsistent. Results from the Baltimore Epidemiologic Catchment Area Study(8) showed that individuals with a history of depressive symptoms had greater risk of fatal or self-reported stroke. In a small scale study from Japan(9), depressive symptoms were associated with an increased incidence of stroke. Similar results have been obtained from Australian(10), Dutch (11, 12), and Swedish (13) studies on the elderly with or without accompanying cardiac disease. However, these findings are in contrast with previous (14, 15) and more recent(16) findings showing that depressive symptoms are not associated with an increased risk of stroke in the elderly. Recent findings from the EPIC-Norfolk study (17) also

showed that major depressive disorder are not associated with incident stroke in a large sample of participants aged 41 to 80 years.

In addition to these controversies, it is noteworthy that epidemiological studies examining the association between depression and cardiovascular disease typically use either CHD or CBVD as the outcome, rarely do they examine them both within the same population (3). This makes it difficult to compare the predictive power of depression for the two outcomes. Such comparison is important because differences in the pathogenesis of atherosclerotic lesions in coronary and cerebral arteries have been shown (18, 19), even though CHD and CBVD are characterized by some common aspects and they share several risk factors. In this report from the Health and Social Support (HeSSup) study, we used prospective data from a large sample of the Finnish population to compare the importance of depression as a risk factor for CHD and CBVD within the same population.

MATERIALS AND METHODS

Population

The Health and Social Support (HeSSup) study is a prospective cohort study on a population sample representative of the Finnish population of the following four age groups: 20-24, 30-34, 40-44, and 50-54 years at baseline in 1998,(20) a total of 10,628 men and 15,267 women. The Turku University Central Hospital Ethics Committee approved the study.

Depression

The Beck Depression Inventory (BDI) was administered to all participants at baseline in 1998. The BDI (21) is a 21-question multiple-choice self-report inventory that is one of the most widely used instruments for measuring the severity of depression. Each item requires a response on a 4-point scale, ranging from 0 to 3 (total scores can range from 0 to 63). A score

of 10 or higher (21) is seen to separate those participants with subclinical mild to severe depression from those without depression.

Prescriptions of antidepressant medications were used as a proxy to capture individuals who were more likely to have more severe depressive symptoms using data from the National-Drug-Prescription-Register data. This register includes out-patient prescription data classified according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification code and tracks medication purchased from all pharmacies in Finland. The personal identification numbers (a unique number assigned to each Finnish citizen) of participants was used to collect data on date of purchase of antidepressants (ATC code N06A), bought on prescriptions that are written only by physicians in Finland. These data were drawn from the register for 1998, i.e., at study baseline, as were responses on the BDI.

Follow-up of Coronary Heart Disease and Cerebrovascular Disease

The personal identification number of participants was used to collect records of hospitalisations from the Finnish National Hospital discharge register and mortality records from the Statistics Finland register. These registers provide virtually complete hospital discharge and mortality data and the associated diagnoses of fatal or non-fatal CHD or CBVD events. The register data have been validated against the population-based myocardial infarction register for classifying events using the 2003 American Heart Association definition.(22) The follow up for CHD and CBVD events involved extracting data on the date and cause of hospitalization and death for all participants who were treated in a hospital or died between January 1, 1999 and December 31, 2005. Disease end point, based on the main diagnoses, was determined by ICD-10 codes I20-I25 (CHD) and ICD-10 codes I60-I69 (CBVD).

Health status at baseline

From the Drug Reimbursement Register, we identified all participants entitled to special reimbursements for medication to hypertension, diabetes and CHD in 1998, i.e., at study baseline, and excluded from this study those with entitlements to special reimbursements for CHD. We also excluded all participants hospitalized for CHD or CBVD in 1998 using the national hospital discharge register. Thus, the remaining sample consisted of participants free of CHD and CBVD at baseline. Data on hypertension and diabetes were used as covariates.

Covariates

All background variables were measured at baseline: sex (male vs. female), age groups (20-24; 30-34; 40-44; 50-54 years) and education (basic, secondary, lower tertiary, higher tertiary). We assessed four behaviour-related risk factors using standard questionnaire measurements in the baseline survey. Smoking status was measured with a dichotomous variable which describes current regular smoking (never- or ex-smoker; current smoker; missing data). The participants reported their habitual frequency and the amount of beer, wine, and spirits consumed. They were classified as having a high alcohol intake if their weekly consumption exceeded 16 drinks (200 g of alcohol) (No vs. Yes). Body mass index (BMI), calculated from self-reported weight and height, was used to measure obesity (BMI $\geq$30 kg/m^2 vs. BMI < 30 kg/m^2). Physical activity was calculated using the Metabolic Equivalent Task (MET) index to measure sedentary life style (<2 MET-hours per day) (No vs. Yes)

Statistical Analysis

Differences in CHD, CBVD and depression (defined as BDI score $\geq$ 10 or filling antidepressant prescriptions) as a function of sample characteristics were assessed using the chi-square test. We examined the relationships between depression and cardiovascular outcomes (CHD and CBVD events) using four serially adjusted Cox regression models. In

model 1, depression and sex, age and education were the sole independent variables. In model 2 and 3, the Hazard Ratios (HRs) were adjusted for behavioural (alcohol consumption, sedentary lifestyle, and smoking) and biological (obesity, hypertension or diabetes, and incident CHD or CBVD) risk factors, respectively. In model 4, the HRs were simultaneously adjusted for all aforementioned covariates. In addition to these analyses, we examined the association between continuous BDI scores to determine the risk of CHD and CBVD associated with a 1-unit increase in BDI. There is no evidence of interactions between depression and sex in relation to CHD and CBVD status ($p>0.05$), allowing us to combine men and women in the analyses. The assumption of proportional hazards assessed examining the time-dependent interaction term between depression and logarithm of the follow-up period (time variable) held (all $p>0.05$).

RESULTS

Of the 25 895 respondents to the baseline survey in 1998, 234 had moved abroad, and could not be included in the follow-up. Data on CHD and CBVD were linked to survey responses from national health registers on the basis of a written consent from 24 128 (93%) participants. A total of 23282 participants with complete data on covariates were included in the analyses. A total of 203 incident CHD events (fatal or non-fatal ischemic heart disease events) and 129 incident CBVD events (fatal and non-fatal stroke events: 27 subarachnoid haemorrhages, 23 intracerebral haemorrhages, 55 cerebral infarction, 3 other nontraumatic intracranial haemorrhage, 19 other cerebrovascular diseases, 2 Sequelae of cerebral infarction) were documented during the follow-up.

Table 1 presents the differences in CHD, CBVD and depression as a function of baseline sample characteristics. CHD and CBVD events were higher in men, older participants, those with lower educational level, current smokers (not for CBVD), high alcohol consumers, obese participants and those with a sedentary life style and with hypertension or diabetes

($p \leq 0.026$). Depression among participants at baseline (BDI score ≥ 10 or filling antidepressant prescriptions) was more likely among women, older, those with a lower education, current smokers, high alcohol consumers, obese, those more likely to have a sedentary life style and those with hypertension or diabetes ($p \leq 0.01$).

Table 2 presents the associations between depression and subsequent CHD and CBVD events using Cox regression analysis. In model 1, when adjusted for sociodemographic variables, the HR for CHD was 1.66 (95% CI 1.24-2.24) for participants with mild to severe depressive symptoms and 2.04 (95% CI 1.27-3.27) for participants who filled antidepressant prescriptions when compared to those without depression markers. The risk of CHD for 1-unit increase in the score on the BDI (continuous variable) was 1.04 (95% CI 1.02-1.06). For CBVD, the HR adjusted for sociodemographic factors was 1.01 (95% CI 0.67-1.53) for participants with mild to severe depressive symptoms, 1.77 (95% CI 0.95-3.29) for those who filled antidepressant prescriptions, and 1.01 (95% CI 0.99-1.04) for 1-unit increase on the BDI (continuous variable). In models 2 and 3, adjusted for behavioural and biological risk factors respectively, these associations were attenuated but the association between depression and CHD was robust to these adjustments. In model 4 including simultaneously adjusted for all aforementioned variables, these associations were further reduced and only the association with CHD remained evident. The corresponding fully adjusted HRs being 1.47 (1.08-1.99) and 1.72 (1.06-2.77) for CHD. For CBVD these HRs were 0.87 (0.57-1.32) and 1.52 (0.81-2.84).

Sensitivity analyses

To test the robustness of our findings, we repeated the analyses excluding CHD and CBVD events that occurred in the first two years of follow-up. These analyses provided a similar pattern of associations as those presented in Table 2. For CHD the number of events was reduced by 31% (n=145), but the unadjusted HR for participants with mild to severe depression (BDI score ≥ 10) and for those who filled prescriptions for antidepressant drugs

remained 2.08 (p<0.001) and 2.15 (*p*<0.006) when compared to those who were not depressed. The corresponding fully adjusted HRs were 1.94 (*p*<0.001) and 2.00 (*p*=0.015). For CBVD the number of events was reduced by 26% (n=97) and the corresponding unadjusted HRs were 1.03 (*p*=0.898) and 1.94 (*p*=0.060). The fully adjusted HRs were 0.89 (*p*=0.626) and 1.66 (*p*=0.155).

We also repeated the analyses excluding definite angina (ICD-10 code I20) events and considering only fatal and non fatal myocardial infarction (n=142). The HRs from model 1 for participants with mild to severe depression (BDI score ≥ 10) and for those who filled prescriptions for antidepressant were 1.95 (p<0.001) and 2.56 (*p*<0.001), respectively, when compared to those who were not depressed. The corresponding fully adjusted HRs were 1.62 (*p*<0.008) and 2.08 (*p*=0.007). These results are highly consistent with those obtained including definite angina, leading us to conclude that the results reported here are not driven by "soft" endpoints.

In addition to these analyses, we examined the association between the severity of depressive symptoms and the risk of CHD and CBVD by using the standard cut-offs as follows (23): scores of 0–9 indicated no depression, 10–18 indicated mild depression, 19–29 indicated moderate and 30–63 indicated severe depression. For CHD, the unadjusted HRs were 1.57 (*p*=0.008) for participants with mild, 1.81 (*p*=0.029) for those with moderate, and 2.80 (*p*=0.042) for those with severe depressive symptoms. The corresponding fully adjusted HRs were 1.45 (p=0.0325), 1.58 (p=0.097), 2.15 (p=0.784). For CBVD, the corresponding unadjusted HRs were 0.93 (*p*=0.7553), 0.99 (*p*=0.684), and 2.68 (*p*=0.094) and fully adjusted HRs were 0.82 (p=0.435), 0.79 (p=0.577), and 1.97 (p=0.255);

DISCUSSION

In this study we sought to compare the predictive power of depression for coronary heart disease (CHD) to that for cerebrovascular disease (CBVD). Using a large population

sample representative of the Finnish population in four age groups, we examined the associations between depression and CHD and CBVD in the same population. Our results show that participants with mild to severe depressive symptoms (Beck depression score ≥ 10) had an increased risk of CHD but not CBVD. The results also show that participants who filled antidepressant prescriptions had an increased risk of CHD but not CBVD. After adjustments for sociodemographics and bio-behavioural risk factors, only the associations between depression and incident CHD remained evident. Similar pattern of associations were observed when the measure of depression was modelled as a continuous variable.

Comparison with previous studies

To the best of our knowledge this is one of the first large aetiological studies to examine the associations of subclinical and clinical depression markers with CHD and CBVD as specific endpoints within the same population of men and women without a history of diagnosed CHD or CBVD events at the study baseline. We found only one study, the Women's Health Initiative study (24), that had examined the influence of depression symptoms for CHD and CBVD as specific endpoints in the same population. Using 6 items from the 20-item Center for Epidemiological Studies Depression Scale (CES-D), the study showed that in older postmenopausal women without a history of CHD or CBVD, depressive symptoms were not associated with an increased risk of incident stroke, unadjusted and adjusted hazard ratio were 1.09 and 1.01, respectively. Their finding is consistent with the present results based on a large population sample representative of the Finnish population in four equally sized age groups ranging from 20 to 54 years. The CHD and CBVD events in our study were ascertained using data on hospitalizations from the Finnish national hospital discharge register and mortality data from the Statistics Finland register. Two validation studies (22, 25) have demonstrated that diagnoses of fatal and non-fatal CHD events and causes of death in these registers were in strong agreement with major coronary event defined by strict criteria, justifying their use as endpoint measures in studies. Strengths of the present study also include the assessment of

depression using both pharmacy refill records of antidepressant medications and a self-reported measure using a validated questionnaire.

Our results showing both markers of depression to be associated with an increased risk of incident CHD is consistent with several prospective studies on healthy people that have demonstrated the predictive value of depression or depressive symptoms for the onset of CHD (4-7). We found the adjusted risk of CHD to be 1.7 for those with clinically significant depression symptoms, broadly consistent with pooled relative risks of CHD of between 1.64 and 1.80 in recent meta-analyses (5-7). It should be noted that we used prescription of antidepressant medication as a proxy measure to capture individuals who were more likely to have clinically significant depression. However, there is some evidence to suggest that some antidepressants influence vascular disease risk (Hippisley-Cox, 2001 #2225) and this might explain the stronger effect between this proxy measure of depression and incident CHD in our study.

We also showed a 1-unit increase in the BDI score to be associated with an excess CHD risk of 3% (or 63% for a 10-unit increase); this suggests that our findings were not sensitive to the specific cut-off used for defining depression using the Beck Depression Inventory. These results are also consistent with the dose-response association found with CHD when focusing only on the severity of depressive symptoms (sensitivity analysis).

As hypertension and/or diabetes are known to influence both mental health and vascular disease risk (26-28), we conducted post hoc analyses stratifying the sample by hypertension and diabetes status. In participants without hypertension and diabetes, sex-age-education adjusted Hazard Ratios (HRs) for CHD was 1.43 (p=0.046) for those with mild to severe depressive symptoms, i.e. scoring 10 or more on the 21-item Beck-Depression-Inventory, and 1.79 (p=0.052) for those who filled antidepressant prescriptions compared to those without these depression markers. The corresponding fully adjusted HRs were 1.31

(p=0.131) and 1.65 (p=0.096). In participants with hypertension and diabetes, sex-age-education adjusted Hazard Ratios (HRs) for CHD was 2.27 (p=0.006) for those with mild to severe depressive symptoms, i.e. scoring 10 or more on the 21-item Beck-Depression-Inventory, and 2.43 (p=0.031) for those who filled antidepressant prescriptions compared to those without these depression markers. The corresponding fully adjusted HRs were 2.67 (p=0.001) and 2.80 (p=0.014). These stratified results provide some evidence that the effect of depression on CHD might be stronger in participants with a history of diagnosed hypertension and diabetes.

We found no consistent evidence of an association between depression symptoms, assessed by the BDI and categorised into a dichotomous variable using the standard cut-off, and CBVD, even in analysis adjusted simply for sociodemographic factors. This finding is consistent with some previous studies examining the association between depression and stroke (14, 15, 17). However, the majority of previous studies (6 out of 9 studies) showing depression to be (10-12) or not to be a risk factor (14-16) for CBVD have been conducted in samples of elderly participants in contrast to our sample of working-aged adults. Two other studies have found depressive symptoms to be associated with an increased risk of stroke, but these findings were based on self-reported stroke (8) or very few stroke events (9). Finally, the EPIC-Norfolk study (17) on 20,627 stroke-free participants (aged 41 to 80 years) with 595 incident stroke endpoints found major depressive disorder not to be associated with incident stroke. In contrast, psychological distress, a more general measure of mental health well-being, was associated with an increased incidence of stroke in that cohort. The authors invoked low prevalence of major depression in their sample as an explanation of the null finding for major depression. Furthermore, assessment of major depressive disorder symptoms was based on a 1-year or lifetime recall, a potential source of bias due to differential recall. The long period of recall may also explain the low prevalence of major depressive disorder in their sample insofar that people might have recovered from their depression"

The present finding showing a stronger predictive power of depression for CHD compared to that for CBVD is relatively novel due to the fact that both endpoints were examined in the same study. There is quite a lot of evidence to support the hypothesis of differential effects of various risk factors, including depression, on CHD and CBVD. There is already some evidence of differences in the relative impact of conventional risk factors for CHD and CBVD. An early study from the Framingham cohort found that high cholesterol levels were an important risk factor for myocardial infarction but not stroke (**29**). In the same vein, more recent large prospective studies have shown that elevated serum cholesterol is a strong risk factor for CHD, but the association with stroke varies depending on the stroke subtype. There is also evidence to suggest that systemic hypertension is a major risk factor for stroke, while its influence on ischemic heart disease is less clear, particularly in the male population (**30**). Furthermore, several prospective studies have reported either a U-shaped or no association between physical activity and stroke (**31**), while current evidence clearly indicates its protective influence on CHD risk (**32**) . Finally, recent guidelines for prevention of stroke suggest that the effect of alcohol and obesity on stroke is complex and controversial, this is in contrast to the known adverse effects on CHD (**33**). Thus, these differences in CHD and CBVD risk factors could be a possible explanation of why depression does not affect them equaally.

Many mechanisms have been proposed to explain how depression may be a risk factor for CHD. Both biological and behavioural mechanisms have been shown to mediate the link between depression and CHD. Depression has been found to be associated with pathophysiological changes which may increase the risk of cardiac morbidity and mortality, including autonomic nervous system dysfunction (e.g., elevated heart rate, low heart rate variability, and exaggerated heart rate responses to physical stressors) (**34**), hypothalamic-pituitary-adrenal axis dysregulation (increased cortisol secretion) (**35**), enhanced inflammatory processes (higher levels of interleukin-6, C-reactive protein and fibrinogen) (**36**) and accelerated progression of atherosclerosis as indicated by change in carotid intima-media

thickness (**37**). Depression could also be linked to CHD via behaviour-related factors (**38**). In our study, depression markers were found to be associated with current smoking, high alcohol intake, obesity and sedentary life style, suggesting that these factors are potential mediators for the association between depression and CHD. Behavioural mediation was also supported by the finding that the association between depression and CHD was reduced when adjusting for behaviour-related factors. However, further research is needed to examine whether depression is related to sustained elevated CHD risk factors trajectories over time and whether it induces episodic elevations in risk factors, such as blood pressure, which could act as a trigger for coronary events among employees with sub-clinical CHD. Some of the CHD risk factors (e.g., high alcohol intake, sedentary life style, and obesity) may also act as confounders by increasing the risk of both depression and CHD. Further studies examining the bidirectional association between biobehavioural CHD risk factors and depression are needed in order to disentangle their temporal sequence.

Limitations

Interpretation of our findings should be considered within the context of the limitations of the study. Firstly, the present study was based on a large population sample representative of the Finnish population in four age groups, but did not include elderly participants which may limit the generalizability of our findings. In particular, this may explain why an association between depression markers and CBVD was not evidenced in the present study. Secondly, cerebrovascular disease end point based on the main diagnosis was defined using ICD-10 codes I60-I69 (i.e. stroke and other cerebrovascular diseases), and did not cover all manifestations of CBVD, which may limit the generalizability of our findings to others types of CBVD such as vascular dementia. Further studies are needed to examine the association between depression and cerebrovascular disease subtypes, such as ischaemic and hemorrhagic stroke**.** Thirdly, we assessed depression only at one point in time in the present study and did

not track the chronicity or course of depression in relation to CHD and CBVD. Nevertheless, additional analyses revealed that the clinically diagnosed depression, based on filled prescriptions for antidepressants drugs, at the end of the study (in 2005) was 3.5 times higher for participants with mild to severe depression symptoms at study baseline. The corresponding odd was 8.6 times higher for those with severe symptoms at this time, suggesting a persistence of depressive symptoms during the follow-up. Moreover, our sensitivity analyses revealed that depression was associated with CHD even after the removal of events occurring in the first two years of follow-up.

Conclusions

In this study on working-age adults from a randomly selected population of Finnish men and women initially free from cardiovascular disease we found that mild to severe depressed participants had an increased risk for CHD over the 7 years of follow-up. There was no clear evidence that depression was associated with the risk of CBVD, but this result needs further confirmation.

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Conflicts of Interest:

None declared.

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Table 1. Number of Incident Coronary Heart Disease, Cerebrovascular Disease, and depression as a function of covariates.

Baseline Covariates	Participants (%)	Coronary Heart Disease (%)	Cerebrovascular Disease (%)	Depression (%) (BDI ≥ 10)*	Antidepressant filled (%)**
All	23282 (100)	203 (0.90)	129 (0.60)	4562 (19.6)	927 (4.0)
Sex					
Men	9507 (41)	145 (1.5)	70 (0.7)	1673 (17.2)	317 (3.2)
Women	13775 (59)	58 (0.4)	59 (0.4)	3031 (21.3)	652 (4.6)
Age-group (years)					
20-24	6333 (27)	1 (0.0)	5 (0.1)	976 (15.4)	100 (1.6)
30-34	5542 (24)	7 (0.1)	9 (0.2)	1021 (18.4)	213 (3.8)
40-44	5575 (24)	44 (0.8)	34 (0.6)	1200 (21.5)	293 (5.3)
50-54	5832 (25)	151 (2.6)	81 (1.4)	1365 (23.6)	321 (5.5)
Education					
Basic	7453 (32)	92 (1.2)	56 (0.8)	1730 (23.2)	376 (5.0)
Secondary	5250 (23)	36 (0.7)	28 (0.5)	1084 (20.6)	179 (3.4)
Lower tertiary	7407 (32)	57 (0.8)	31 (0.4)	1275 (17.2)	251 (3.4)
Higher tertiary	3172 (14)	18 (0.6)	14 (0.4)	473 (14.9)	121 (3.8)
Current smoker					
No	15547 (67)	105 (0.7)	77 (0.5)	2665 (17.1)	526 (3.4)
Yes	5878 (25)	86 (1.5)	43 (0.7)	1565 (26.6)	329 (5.6)
Missing	1857 (8)	12 (0.6)	9 (0.5)	332 (17.9)	72 (3.9)
High alcohol intake (≥200 g/week)					
No	21017 (90)	167 (0.8)	109 (0.5)	3876 (18.4)	785 (3.7)
Yes	2265 (10)	37 (1.6)	20 (0.9)	686 (30.3)	142 (6.3)
Obesity (BMI≥30)					
No	21050 (90)	167 (0.8)	106 (0.5)	3896 (18.5)	773 (3.7)
Yes	2232 (10)	36 (1.6)	23 (1.0)	666 (29.8)	154 (6.9)
Sedentary life style (<2 MET hours/day)					
No	17903 (77)	133 (0.7)	85 (0.5)	3173 (17.7)	632 (3.5)
Yes	5379 (23)	70 (1.3)	44 (0.8)	1389 (25.8)	295 (5.5)
Hypertension or diabetes					
No	22201 (95)	159 (0.7)	102 (0.5)	4242 (19.1)	840 (3.8)
Yes	1081 (5)	44 (4.1)	27 (2.5)	320 (29.9)	87 (8.0)

All associations were significant at $p \leq 0.026$, except for the association between smoking and CBVD.
* BDI = Beck Depression Inventory score ≥ 10
** Participants who filled prescriptions for antidepressant drugs identified from the National-Prescription-Register

Table 2. Depression as a predictor of Coronary Heart Disease and Cerebrovascular Disease.

Depression	Coronary Heart Disease		Cerebrovascular disease	
	N events/N participants	**HR (95% CI)**	N events/N participants	**HR (95% CI)**
Model 1				
Not depressed (BDI ≤ 9)	138/18720	1.00	100/18720	1.00
Depressed (BDI ≥10)	65/4562	1.66 (1.24-2.24)***	29/4562	1.01 (0.67-1.53)
BDI score (continuous)	203/23282	1.04 (1.02-1.06)***	129/23282	1.01 (0.99-1.04)
Filled antidepressant prescriptions	19/963	2.04 (1.27-3.27)**	11/959	1.77 (0.95-3.29)
Model 2				
Not depressed (BDI ≤ 9)	138/18720	1.00	100/18720	1.00
Depressed (BDI ≥10)	65/4562	1.51 (1.11-2.03)**	29/4562	0.92 (0.61-1.40)
BDI score (continuous)	203/23282	1.04 (1.02-1.06)***	129/23282	1.01 (0.98-1.04)
Filled antidepressant prescriptions	19/963	1.86 (1.15-2.99)**	11/959	1.61 (0.86-3.00)
Model 3				
Not depressed (BDI ≤ 9)	138/18720	1.00	100/18720	1.00
Depressed (BDI ≥10)	65/4562	1.62 (1.20-2.18)***	29/4562	0.93 (0.60-1.42)
BDI score (continuous)	203/23282	1.04 (1.02-1.06)***	129/23282	0.98 (0.96-1.01)
Filled antidepressant prescriptions	19/963	1.89 (1.18-3.05)**	11/959	1.61 (0.86-3.00)
Model 4				
Not depressed (BDI ≤ 9)	138/18720	1.00	100/18720	1.00
Depressed (BDI ≥10)	65/4562	1.47 (1.08-1.99)**	29/4562	0.87(0.57-1.32)
BDI score (continuous)	203/23282	1.03 (1.02-1.05)***	129/23282	0.98 (0.95-1.00)
Filled antidepressant prescriptions	19/927	1.72 (1.06-2.77)*	11/927	1.52(0.81-2.84)

* p<0.05, ** p<0.01, *** p<0.001

Model 1 = hazard ratio (HR) adjusted for sex, age and education.

Model 2 = model 1 additionally adjusted for alcohol consumption, sedentary lifestyle, and smoking.

Model 3 = model 1 additionally adjusted for obesity, hypertension or diabetes, and incident coronary heart disease or incident cerebrovascular disease

Model 4 = HR adjusted for all aforementioned variables