



**HAL**  
open science

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

Hermann Nabi, Mika Kivimaki, Sakari Suominen, Markku Koskenvuo, Archana Singh-Manoux, Jussi Vahtera

► **To cite this version:**

Hermann Nabi, Mika Kivimaki, Sakari Suominen, Markku Koskenvuo, Archana Singh-Manoux, et al.. Does Depression Predict Coronary Heart Disease and Cerebrovascular Disease Equally Well? The HeSSup Prospective Cohort Study. *International Journal of Epidemiology*, 2010, 10.1093/ije/DYQ050 . hal-00581854

**HAL Id: hal-00581854**

**<https://hal.science/hal-00581854>**

Submitted on 1 Apr 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Journal:	<i>International Journal of Epidemiology</i>
Manuscript ID:	IJE-2009-09-0801.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	02-Dec-2009
Complete List of Authors:	Nabi, Hermann; INSERM Kivimaki, Mika; University College London, Department of PEpidemiology & Public Health Suominen, Sakari; University of Turku, Finland, Department of Public Health koskenvuo, markku; University of Helsinki, Finland, Department of Public Health Singh-Manoux, Archana; INSERM, U687 Vahtera, Jussi; Finnish Institute of Occupational Health
Key Words:	Depression, Coronary Heart Disease, Cerebrovascular Disease

1  
2  
3 **Does Depression Predict Coronary Heart Disease and Cerebrovascular Disease Equally**  
4 **Well? The HeSSup Prospective Cohort Study**  
5  
6  
7  
8  
9

10  
11  
12 **Running Head:** Depression, Coronary heart and cerebrovascular diseases  
13  
14  
15  
16  
17

18 Hermann Nabi, PhD<sup>1\*</sup>  
19 Mika Kivimäki, PhD<sup>2</sup>,  
20 Sakari Suominen, MD<sup>3</sup>  
21 Markku Koskenvuo, MD PhD<sup>4</sup>  
22 Archana Singh-Manoux, PhD<sup>1,2,5</sup>  
23 Jussi Vahtera, MD PhD<sup>6</sup>  
24  
25  
26  
27  
28  
29  
30  
31  
32

- 33 1. INSERM U687-IFR69, Villejuif, F-94807 France.  
34 2. Department of Epidemiology and Public Health, University College London, United Kingdom  
35 3. Department of Public Health, University of Turku, Finland  
36 4. Department of Public Health, University of Helsinki, Finland  
37 5. Hôpital Ste Péline, Centre de Gérontologie, Paris, F-75781, France  
38 6. Finnish Institute of Occupational Health, Turku, Finland  
39  
40  
41  
42  
43  
44

45 **Words counts:**

46 Abstract = 241

47 Manuscript = 3904  
48  
49  
50  
51

52 \*Corresponding Author:

53 INSERM Unité 687

54 Hôpital Paul Brousse

55 Bâtiment 15/16

56 16 avenue Paul Vaillant Couturier

57 94807 Villejuif Cedex

58 Email: [Hermann.Nabi@inserm.fr](mailto:Hermann.Nabi@inserm.fr)  
59  
60

## 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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**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.

For Review Only

## 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

1  
2  
3 showed that major depressive disorder are not associated with incident stroke in a large sample  
4  
5 of participants aged 41 to 80 years.  
6  
7

8  
9 In addition to these controversies, it is noteworthy that epidemiological studies  
10  
11 examining the association between depression and cardiovascular disease typically use either  
12  
13 CHD or CBVD as the outcome, rarely do they examine them both within the same population  
14  
15 (3). This makes it difficult to compare the predictive power of depression for the two  
16  
17 outcomes. Such comparison is important because differences in the pathogenesis of  
18  
19 atherosclerotic lesions in coronary and cerebral arteries have been shown (18, 19), even though  
20  
21 CHD and CBVD are characterized by some common aspects and they share several risk  
22  
23 factors. In this report from the Health and Social Support (HeSSup) study, we used prospective  
24  
25 data from a large sample of the Finnish population to compare the importance of depression as  
26  
27 a risk factor for CHD and CBVD within the same population.  
28  
29  
30  
31  
32  
33  
34  
35

## 36 **MATERIALS AND METHODS**

### 37 **Population**

38  
39 The Health and Social Support (HeSSup) study is a prospective cohort study on a  
40  
41 population sample representative of the Finnish population of the following four age groups:  
42  
43 20-24, 30-34, 40-44, and 50-54 years at baseline in 1998,(20) a total of 10,628 men and 15,267  
44  
45 women. The Turku University Central Hospital Ethics Committee approved the study.  
46  
47  
48  
49

### 50 **Depression**

51  
52 The Beck Depression Inventory (BDI) was administered to all participants at baseline  
53  
54 in 1998. The BDI (21) is a 21-question multiple-choice self-report inventory that is one of the  
55  
56 most widely used instruments for measuring the severity of depression. Each item requires a  
57  
58 response on a 4-point scale, ranging from 0 to 3 (total scores can range from 0 to 63). A score  
59  
60

1  
2  
3 of 10 or higher (21) is seen to separate those participants with subclinical mild to severe  
4  
5 depression from those without depression.  
6

7  
8 Prescriptions of antidepressant medications were used as a proxy to capture individuals  
9  
10 who were more likely to have more severe depressive symptoms using data from the National-  
11  
12 Drug-Prescription-Register data. This register includes out-patient prescription data classified  
13  
14 according to the World Health Organization's Anatomical Therapeutic Chemical (ATC)  
15  
16 classification code and tracks medication purchased from all pharmacies in Finland. The  
17  
18 personal identification numbers (a unique number assigned to each Finnish citizen) of  
19  
20 participants was used to collect data on date of purchase of antidepressants (ATC code N06A),  
21  
22 bought on prescriptions that are written only by physicians in Finland. These data were drawn  
23  
24 from the register for 1998, i.e., at study baseline, as were responses on the BDI.  
25  
26  
27  
28  
29  
30

### 31 **Follow-up of Coronary Heart Disease and Cerebrovascular Disease**

32  
33 The personal identification number of participants was used to collect records of  
34  
35 hospitalisations from the Finnish National Hospital discharge register and mortality records  
36  
37 from the Statistics Finland register. These registers provide virtually complete hospital  
38  
39 discharge and mortality data and the associated diagnoses of fatal or non-fatal CHD or CBVD  
40  
41 events. The register data have been validated against the population-based myocardial  
42  
43 infarction register for classifying events using the 2003 American Heart Association  
44  
45 definition.(22) The follow up for CHD and CBVD events involved extracting data on the date  
46  
47 and cause of hospitalization and death for all participants who were treated in a hospital or died  
48  
49 between January 1, 1999 and December 31, 2005. Disease end point, based on the main  
50  
51 diagnoses, was determined by ICD-10 codes I20-I25 (CHD) and ICD-10 codes I60-I69  
52  
53 (CBVD).  
54  
55  
56  
57  
58  
59  
60



## 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<sup>2</sup> vs. BMI < 30 kg/m<sup>2</sup>). 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

1  
2  
3 model 1, depression and sex, age and education were the sole independent variables. In model  
4  
5 2 and 3, the Hazard Ratios (HRs) were adjusted for behavioural (alcohol consumption,  
6  
7 sedentary lifestyle, and smoking) and biological (obesity, hypertension or diabetes, and  
8  
9 incident CHD or CBVD) risk factors, respectively. In model 4, the HRs were simultaneously  
10  
11 adjusted for all aforementioned covariates. In addition to these analyses, we examined the  
12  
13 association between continuous BDI scores to determine the risk of CHD and CBVD  
14  
15 associated with a 1-unit increase in BDI. There is no evidence of interactions between  
16  
17 depression and sex in relation to CHD and CBVD status ( $p>0.05$ ), allowing us to combine men  
18  
19 and women in the analyses. The assumption of proportional hazards assessed examining the  
20  
21 time-dependent interaction term between depression and logarithm of the follow-up period  
22  
23 (time variable) held (all  $p>0.05$ ).  
24  
25  
26  
27  
28  
29  
30

## 31 RESULTS

32  
33 Of the 25 895 respondents to the baseline survey in 1998, 234 had moved abroad, and  
34  
35 could not be included in the follow-up. Data on CHD and CBVD were linked to survey  
36  
37 responses from national health registers on the basis of a written consent from 24 128 (93%)  
38  
39 participants. A total of 23282 participants with complete data on covariates were included in  
40  
41 the analyses. A total of 203 incident CHD events (fatal or non-fatal ischemic heart disease  
42  
43 events) and 129 incident CBVD events (fatal and non-fatal stroke events: 27 subarachnoid  
44  
45 haemorrhages, 23 intracerebral haemorrhages, 55 cerebral infarction, 3 other nontraumatic  
46  
47 intracranial haemorrhage, 19 other cerebrovascular diseases, 2 Sequelae of cerebral infarction)  
48  
49 were documented during the follow-up.  
50  
51  
52  
53  
54

55 Table 1 presents the differences in CHD, CBVD and depression as a function of  
56  
57 baseline sample characteristics. CHD and CBVD events were higher in men, older participants,  
58  
59 those with lower educational level, current smokers (not for CBVD), high alcohol consumers,  
60  
obese participants and those with a sedentary life style and with hypertension or diabetes

1  
2  
3 ( $p \leq 0.026$ ). Depression among participants at baseline (BDI score  $\geq 10$  or filling antidepressant  
4  
5 prescriptions) was more likely among women, older, those with a lower education, current  
6  
7 smokers, high alcohol consumers, obese, those more likely to have a sedentary life style and  
8  
9 those with hypertension or diabetes ( $p \leq 0.01$ ).

10  
11  
12  
13 Table 2 presents the associations between depression and subsequent CHD and CBVD events  
14  
15 using Cox regression analysis. In model 1, when adjusted for sociodemographic variables, the  
16  
17 HR for CHD was 1.66 (95% CI 1.24-2.24) for participants with mild to severe depressive  
18  
19 symptoms and 2.04 (95% CI 1.27-3.27) for participants who filled antidepressant prescriptions  
20  
21 when compared to those without depression markers. The risk of CHD for 1-unit increase in  
22  
23 the score on the BDI (continuous variable) was 1.04 (95% CI 1.02-1.06). For CBVD, the HR  
24  
25 adjusted for sociodemographic factors was 1.01 (95% CI 0.67-1.53) for participants with mild  
26  
27 to severe depressive symptoms, 1.77 (95% CI 0.95-3.29) for those who filled antidepressant  
28  
29 prescriptions, and 1.01 (95% CI 0.99-1.04) for 1-unit increase on the BDI (continuous  
30  
31 variable). In models 2 and 3, adjusted for behavioural and biological risk factors respectively,  
32  
33 these associations were attenuated but the association between depression and CHD was robust  
34  
35 to these adjustments. In model 4 including simultaneously adjusted for all aforementioned  
36  
37 variables, these associations were further reduced and only the association with CHD remained  
38  
39 evident. The corresponding fully adjusted HRs being 1.47 (1.08-1.99) and 1.72 (1.06-2.77) for  
40  
41 CHD. For CBVD these HRs were 0.87 (0.57-1.32) and 1.52 (0.81-2.84).

## 50 Sensitivity analyses

51  
52 To test the robustness of our findings, we repeated the analyses excluding CHD and  
53  
54 CBVD events that occurred in the first two years of follow-up. These analyses provided a  
55  
56 similar pattern of associations as those presented in Table 2. For CHD the number of events  
57  
58 was reduced by 31% ( $n=145$ ), but the unadjusted HR for participants with mild to severe  
59  
60 depression (BDI score  $\geq 10$ ) and for those who filled prescriptions for antidepressant drugs

1  
2  
3 remained 2.08 ( $p<0.001$ ) and 2.15 ( $p<0.006$ ) when compared to those who were not depressed.  
4  
5 The corresponding fully adjusted HRs were 1.94 ( $p<0.001$ ) and 2.00 ( $p=0.015$ ). For CBVD the  
6  
7 number of events was reduced by 26% ( $n=97$ ) and the corresponding unadjusted HRs were  
8  
9 1.03 ( $p=0.898$ ) and 1.94 ( $p=0.060$ ). The fully adjusted HRs were 0.89 ( $p=0.626$ ) and 1.66  
10  
11 ( $p=0.155$ ).  
12  
13

14  
15 We also repeated the analyses excluding definite angina (ICD-10 code I20) events and  
16  
17 considering only fatal and non fatal myocardial infarction ( $n=142$ ). The HRs from model 1 for  
18  
19 participants with mild to severe depression (BDI score  $\geq 10$ ) and for those who filled  
20  
21 prescriptions for antidepressant were 1.95 ( $p<0.001$ ) and 2.56 ( $p<0.001$ ), respectively, when  
22  
23 compared to those who were not depressed. The corresponding fully adjusted HRs were 1.62  
24  
25 ( $p<0.008$ ) and 2.08 ( $p=0.007$ ). These results are highly consistent with those obtained  
26  
27 including definite angina, leading us to conclude that the results reported here are not driven by  
28  
29 “soft” endpoints.  
30  
31  
32

33  
34 In addition to these analyses, we examined the association between the severity of  
35  
36 depressive symptoms and the risk of CHD and CBVD by using the standard cut-offs as follows  
37  
38 (23): scores of 0–9 indicated no depression, 10–18 indicated mild depression, 19–29 indicated  
39  
40 moderate and 30–63 indicated severe depression. For CHD, the unadjusted HRs were 1.57  
41  
42 ( $p=0.008$ ) for participants with mild, 1.81 ( $p=0.029$ ) for those with moderate, and 2.80  
43  
44 ( $p=0.042$ ) for those with severe depressive symptoms. The corresponding fully adjusted HRs  
45  
46 were 1.45 ( $p=0.0325$ ), 1.58 ( $p=0.097$ ), 2.15 ( $p=0.784$ ). For CBVD, the corresponding  
47  
48 unadjusted HRs were 0.93 ( $p=0.7553$ ), 0.99 ( $p=0.684$ ), and 2.68 ( $p=0.094$ ) and fully adjusted  
49  
50 HRs were 0.82 ( $p=0.435$ ), 0.79 ( $p=0.577$ ), and 1.97 ( $p=0.255$ );  
51  
52  
53  
54  
55

## 56 57 **DISCUSSION**

58  
59 In this study we sought to compare the predictive power of depression for coronary  
60  
heart disease (CHD) to that for cerebrovascular disease (CBVD). Using a large population

1  
2  
3 sample representative of the Finnish population in four age groups, we examined the  
4  
5 associations between depression and CHD and CBVD in the same population. Our results  
6  
7 show that participants with mild to severe depressive symptoms (Beck depression score  $\geq 10$ )  
8  
9 had an increased risk of CHD but not CBVD. The results also show that participants who filled  
10  
11 antidepressant prescriptions had an increased risk of CHD but not CBVD. After adjustments  
12  
13 for sociodemographics and bio-behavioural risk factors, only the associations between  
14  
15 depression and incident CHD remained evident. Similar pattern of associations were observed  
16  
17 when the measure of depression was modelled as a continuous variable.  
18  
19  
20  
21

### 22 **Comparison with previous studies**

23  
24 To the best of our knowledge this is one of the first large aetiological studies to  
25  
26 examine the associations of subclinical and clinical depression markers with CHD and CBVD  
27  
28 as specific endpoints within the same population of men and women without a history of  
29  
30 diagnosed CHD or CBVD events at the study baseline. We found only one study, the Women's  
31  
32 Health Initiative study (24), that had examined the influence of depression symptoms for CHD  
33  
34 and CBVD as specific endpoints in the same population. Using 6 items from the 20-item  
35  
36 Center for Epidemiological Studies Depression Scale (CES-D), the study showed that in older  
37  
38 postmenopausal women without a history of CHD or CBVD, depressive symptoms were not  
39  
40 associated with an increased risk of incident stroke, unadjusted and adjusted hazard ratio were  
41  
42 1.09 and 1.01, respectively. Their finding is consistent with the present results based on a large  
43  
44 population sample representative of the Finnish population in four equally sized age groups  
45  
46 ranging from 20 to 54 years. The CHD and CBVD events in our study were ascertained using  
47  
48 data on hospitalizations from the Finnish national hospital discharge register and mortality data  
49  
50 from the Statistics Finland register. Two validation studies (22, 25) have demonstrated that  
51  
52 diagnoses of fatal and non-fatal CHD events and causes of death in these registers were in  
53  
54 strong agreement with major coronary event defined by strict criteria, justifying their use as  
55  
56 endpoint measures in studies. Strengths of the present study also include the assessment of  
57  
58  
59  
60

1  
2  
3 depression using both pharmacy refill records of antidepressant medications and a self-reported  
4  
5 measure using a validated questionnaire.  
6  
7

8 Our results showing both markers of depression to be associated with an increased risk  
9  
10 of incident CHD is consistent with several prospective studies on healthy people that have  
11  
12 demonstrated the predictive value of depression or depressive symptoms for the onset of CHD  
13  
14 (4-7). We found the adjusted risk of CHD to be 1.7 for those with clinically significant  
15  
16 depression symptoms, broadly consistent with pooled relative risks of CHD of between 1.64  
17  
18 and 1.80 in recent meta-analyses (5-7). It should be noted that we used prescription of  
19  
20 antidepressant medication as a proxy measure to capture individuals who were more likely to  
21  
22 have clinically significant depression. However, there is some evidence to suggest that some  
23  
24 antidepressants influence vascular disease risk (Hippisley-Cox, 2001 #2225) and this might  
25  
26 explain the stronger effect between this proxy measure of depression and incident CHD in our  
27  
28 study.  
29  
30  
31  
32  
33

34 We also showed a 1-unit increase in the BDI score to be associated with an excess  
35  
36 CHD risk of 3% (or 63% for a 10-unit increase); this suggests that our findings were not  
37  
38 sensitive to the specific cut-off used for defining depression using the Beck Depression  
39  
40 Inventory. These results are also consistent with the dose-response association found with  
41  
42 CHD when focusing only on the severity of depressive symptoms (sensitivity analysis).  
43  
44  
45

46 As hypertension and/or diabetes are known to influence both mental health and  
47  
48 vascular disease risk (26-28), we conducted post hoc analyses stratifying the sample by  
49  
50 hypertension and diabetes status. In participants without hypertension and diabetes, sex-age-  
51  
52 education adjusted Hazard Ratios (HRs) for CHD was 1.43 (p=0.046) for those with mild to  
53  
54 severe depressive symptoms, i.e. scoring 10 or more on the 21-item Beck-Depression-  
55  
56 Inventory, and 1.79 (p=0.052) for those who filled antidepressant prescriptions compared to  
57  
58 those without these depression markers. The corresponding fully adjusted HRs were 1.31  
59  
60

1  
2  
3 (p=0.131) and 1.65 (p=0.096). In participants with hypertension and diabetes, sex-age-  
4  
5 education adjusted Hazard Ratios (HRs) for CHD was 2.27 (p=0.006) for those with mild to  
6  
7 severe depressive symptoms, i.e. scoring 10 or more on the 21-item Beck-Depression-  
8  
9 Inventory, and 2.43 (p=0.031) for those who filled antidepressant prescriptions compared to  
10  
11 those without these depression markers. The corresponding fully adjusted HRs were 2.67  
12  
13 (p=0.001) and 2.80 (p=0.014). These stratified results provide some evidence that the effect of  
14  
15 depression on CHD might be stronger in participants with a history of diagnosed hypertension  
16  
17 and diabetes.  
18  
19  
20

21  
22 We found no consistent evidence of an association between depression symptoms,  
23  
24 assessed by the BDI and categorised into a dichotomous variable using the standard cut-off,  
25  
26 and CBVD, even in analysis adjusted simply for sociodemographic factors. This finding is  
27  
28 consistent with some previous studies examining the association between depression and stroke  
29  
30 (14, 15, 17). However, the majority of previous studies (6 out of 9 studies) showing depression  
31  
32 to be (10-12) or not to be a risk factor (14-16) for CBVD have been conducted in samples of  
33  
34 elderly participants in contrast to our sample of working-aged adults. Two other studies have  
35  
36 found depressive symptoms to be associated with an increased risk of stroke, but these findings  
37  
38 were based on self-reported stroke (8) or very few stroke events (9). Finally, the EPIC-Norfolk  
39  
40 study (17) on 20,627 stroke-free participants (aged 41 to 80 years) with 595 incident stroke  
41  
42 endpoints found major depressive disorder not to be associated with incident stroke. In  
43  
44 contrast, psychological distress, a more general measure of mental health well-being, was  
45  
46 associated with an increased incidence of stroke in that cohort. The authors invoked low  
47  
48 prevalence of major depression in their sample as an explanation of the null finding for major  
49  
50 depression. Furthermore, assessment of major depressive disorder symptoms was based on a 1-  
51  
52 year or lifetime recall, a potential source of bias due to differential recall. The long period of  
53  
54 recall may also explain the low prevalence of major depressive disorder in their sample insofar  
55  
56 that people might have recovered from their depression”  
57  
58  
59  
60

1  
2  
3 The present finding showing a stronger predictive power of depression for CHD  
4  
5 compared to that for CBVD is relatively novel due to the fact that both endpoints were  
6  
7 examined in the same study. There is quite a lot of evidence to support the hypothesis of  
8  
9 differential effects of various risk factors, including depression, on CHD and CBVD. There is  
10  
11 already some evidence of differences in the relative impact of conventional risk factors for  
12  
13 CHD and CBVD. An early study from the Framingham cohort found that high cholesterol  
14  
15 levels were an important risk factor for myocardial infarction but not stroke (29). In the same  
16  
17 vein, more recent large prospective studies have shown that elevated serum cholesterol is a  
18  
19 strong risk factor for CHD, but the association with stroke varies depending on the stroke  
20  
21 subtype. There is also evidence to suggest that systemic hypertension is a major risk factor for  
22  
23 stroke, while its influence on ischemic heart disease is less clear, particularly in the male  
24  
25 population (30). Furthermore, several prospective studies have reported either a U-shaped or no  
26  
27 association between physical activity and stroke (31), while current evidence clearly indicates  
28  
29 its protective influence on CHD risk (32). Finally, recent guidelines for prevention of stroke  
30  
31 suggest that the effect of alcohol and obesity on stroke is complex and controversial, this is in  
32  
33 contrast to the known adverse effects on CHD (33). Thus, these differences in CHD and CBVD  
34  
35 risk factors could be a possible explanation of why depression does not affect them equally.  
36  
37  
38  
39  
40  
41  
42

43 Many mechanisms have been proposed to explain how depression may be a risk factor  
44  
45 for CHD. Both biological and behavioural mechanisms have been shown to mediate the link  
46  
47 between depression and CHD. Depression has been found to be associated with  
48  
49 pathophysiological changes which may increase the risk of cardiac morbidity and mortality,  
50  
51 including autonomic nervous system dysfunction (e.g., elevated heart rate, low heart rate  
52  
53 variability, and exaggerated heart rate responses to physical stressors) (34), hypothalamic-  
54  
55 pituitary-adrenal axis dysregulation (increased cortisol secretion) (35), enhanced inflammatory  
56  
57 processes (higher levels of interleukin-6, C-reactive protein and fibrinogen) (36) and  
58  
59 accelerated progression of atherosclerosis as indicated by change in carotid intima-media  
60



1  
2  
3 thickness (37). Depression could also be linked to CHD via behaviour-related factors (38). In  
4  
5 our study, depression markers were found to be associated with current smoking, high alcohol  
6  
7 intake, obesity and sedentary life style, suggesting that these factors are potential mediators for  
8  
9 the association between depression and CHD. Behavioural mediation was also supported by  
10  
11 the finding that the association between depression and CHD was reduced when adjusting for  
12  
13 behaviour-related factors. However, further research is needed to examine whether depression  
14  
15 is related to sustained elevated CHD risk factors trajectories over time and whether it induces  
16  
17 episodic elevations in risk factors, such as blood pressure, which could act as a trigger for  
18  
19 coronary events among employees with sub-clinical CHD. Some of the CHD risk factors (e.g.,  
20  
21 high alcohol intake, sedentary life style, and obesity) may also act as confounders by increasing  
22  
23 the risk of both depression and CHD. Further studies examining the bidirectional association  
24  
25 between biobehavioural CHD risk factors and depression are needed in order to disentangle  
26  
27 their temporal sequence.  
28  
29  
30  
31  
32  
33  
34

### 35 **Limitations**

36  
37 Interpretation of our findings should be considered within the context of the limitations  
38  
39 of the study. Firstly, the present study was based on a large population sample representative of  
40  
41 the Finnish population in four age groups, but did not include elderly participants which may  
42  
43 limit the generalizability of our findings. In particular, this may explain why an association  
44  
45 between depression markers and CBVD was not evidenced in the present study. Secondly,  
46  
47 cerebrovascular disease end point based on the main diagnosis was defined using ICD-10  
48  
49 codes I60-I69 (i.e. stroke and other cerebrovascular diseases), and did not cover all  
50  
51 manifestations of CBVD, which may limit the generalizability of our findings to others types  
52  
53 of CBVD such as vascular dementia. Further studies are needed to examine the association  
54  
55 between depression and cerebrovascular disease subtypes, such as ischaemic and hemorrhagic  
56  
57 stroke. Thirdly, we assessed depression only at one point in time in the present study and did  
58  
59  
60

1  
2  
3 not track the chronicity or course of depression in relation to CHD and CBVD. Nevertheless,  
4  
5 additional analyses revealed that the clinically diagnosed depression, based on filled  
6  
7 prescriptions for antidepressants drugs, at the end of the study (in 2005) was 3.5 times higher  
8  
9 for participants with mild to severe depression symptoms at study baseline. The corresponding  
10  
11 odd was 8.6 times higher for those with severe symptoms at this time, suggesting a persistence  
12  
13 of depressive symptoms during the follow-up. Moreover, our sensitivity analyses revealed that  
14  
15 depression was associated with CHD even after the removal of events occurring in the first two  
16  
17 years of follow-up.  
18  
19  
20  
21  
22

### 23 **Conclusions**

24  
25 In this study on working-age adults from a randomly selected population of Finnish  
26  
27 men and women initially free from cardiovascular disease we found that mild to severe  
28  
29 depressed participants had an increased risk for CHD over the 7 years of follow-up. There was  
30  
31 no clear evidence that depression was associated with the risk of CBVD, but this result needs  
32  
33 further confirmation.  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Sources of funding**

The study was supported by the Academy of Finland (projects #117604, #124271, #124322, #128089 and #129262), and the Association for Promotion of Occupational Health. We thank these instances, as well as those who kindly volunteered to participate in our study. MK is supported by the BUPA Foundation, UK and the National Heart, Lung, and Blood Institute (R01HL036310-20A2), NIH, US. AS-M is supported by a 'EURYI' award from the European Science Foundation and the national Institute on Aging, NIH (R01AG013196; R01AG034454). The funding agencies played no role in the design, conduct, data management, analysis, or manuscript preparation related to this article. HN had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Conflicts of Interest:**

None declared.

## REFERENCES

1. Mackay J, Mensah GA. *The Atlas of Heart Disease and Stroke*: World Health Organization; 2004.
2. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**(9438): 937-52.
3. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 1998;**55**(7): 580-92.
4. Frasure-Smith N, Lesperance F. Depression--a cardiac risk factor in search of a treatment. *Jama* 2003;**289**(23): 3171-3.
5. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J* 2006;**27**(23): 2763-74.
6. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. *Am J Prev Med* 2002;**23**(1): 51-61.
7. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med* 2003;**65**(2): 201-10.
8. Larson SL, Owens PL, Ford D, Eaton W. Depressive disorder, dysthymia, and risk of stroke: thirteen-year follow-up from the Baltimore epidemiologic catchment area study. *Stroke* 2001;**32**(9): 1979-83.
9. Ohira T, Iso H, Satoh S, et al. Prospective study of depressive symptoms and risk of stroke among japanese. *Stroke* 2001;**32**(4): 903-8.
10. Simons LA, McCallum J, Friedlander Y, Simons J. Risk factors for ischemic stroke: Dubbo Study of the elderly. *Stroke* 1998;**29**(7): 1341-6.
11. Bos MJ, Linden T, Koudstaal PJ, et al. Depressive symptoms and risk of stroke: the Rotterdam Study. *J Neurol Neurosurg Psychiatry* 2008;**79**(9): 997-1001.
12. Wouts L, Oude Voshaar RC, Bremmer MA, Buitelaar JK, Penninx BW, Beekman AT. Cardiac disease, depressive symptoms, and incident stroke in an elderly population. *Arch Gen Psychiatry* 2008;**65**(5): 596-602.
13. Liebetrau M, Steen B, Skoog I. Depression as a risk factor for the incidence of first-ever stroke in 85-year-olds. *Stroke*; **39**(7): 1960-5.
14. Colantonio A, Kasi SV, Ostfeld AM. Depressive symptoms and other psychosocial factors as predictors of stroke in the elderly. *Am J Epidemiol* 1992;**136**(7): 884-94.
15. Colantonio A, Kasl SV, Ostfeld AM, Berkman LF. Psychosocial predictors of stroke outcomes in an elderly population. *J Gerontol* 1993;**48**(5): S261-8.
16. Salaycik KJ, Kelly-Hayes M, Beiser A, et al. Depressive symptoms and risk of stroke: the Framingham Study. *Stroke* 2007;**38**(1): 16-21.
17. Surtees PG, Wainwright NW, Luben RN, Wareham NJ, Bingham SA, Khaw KT. Psychological distress, major depressive disorder, and risk of stroke. *Neurology* 2008;**70**(10): 788-94.
18. Harmsen P, Rosengren A, Tsiopogianni A, Wilhelmsen L. Risk factors for stroke in middle-aged men in Goteborg, Sweden. *Stroke* 1990;**21**(2): 223-9.
19. Wilhelmsen L, Koster M, Harmsen P, Lappas G. Differences between coronary disease and stroke in incidence, case fatality, and risk factors, but few differences in risk factors for fatal and non-fatal events. *Eur Heart J* 2005;**26**(18): 1916-22.
20. Korkeila K, Suominen S, Ahvenainen J, et al. Non-response and related factors in a nation-wide health survey. *Eur J Epidemiol* 2001;**17**(11): 991-9.

- 1
- 2
- 3 21. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring
- 4 depression. *Arch Gen Psychiatry* 1961;**4**: 561-71.
- 5 22. Pajunen P, Koukkunen H, Ketonen M, et al. The validity of the Finnish Hospital
- 6 Discharge Register and Causes of Death Register data on coronary heart disease. *Eur J*
- 7 *Cardiovasc Prev Rehabil* 2005;**12**(2): 132-7.
- 8 23. Beck AT. *Depression; Causes and Treatment*: University of Pennsylvania Press
- 9 Philadelphia, PA;; 1972.
- 10 24. Wassertheil-Smoller S, Shumaker S, Ockene J, et al. Depression and cardiovascular
- 11 sequelae in postmenopausal women. The Women's Health Initiative (WHI). *Arch Intern Med*
- 12 2004;**164**(3): 289-98.
- 13 25. Rapola JM, Virtamo J, Korhonen P, et al. Validity of diagnoses of major coronary
- 14 events in national registers of hospital diagnoses and deaths in Finland. *Eur J Epidemiol* 1997
- 15 ;**13**(2): 133-8.
- 16 26. Kivimaki M, Tabak AG, Batty GD, et al. Hyperglycemia, type 2 diabetes, and
- 17 depressive symptoms: the British Whitehall II study. *Diabetes Care* 2009;**32**(10): 1867-9.
- 18 27. Axon RN, Zhao Y, Egede LE. Association of Depressive Symptoms With All-Cause
- 19 and Ischemic Heart Disease Mortality in Adults With Self-Reported Hypertension. *Am J*
- 20 *Hypertens* 2009 Nov 5.
- 21 28. Vaccaro O, Stamler J, Neaton JD. Sixteen-year coronary mortality in black and white
- 22 men with diabetes screened for the Multiple Risk Factor Intervention Trial (MRFIT). *Int J*
- 23 *Epidemiol* 1998;**27**(4): 636-41.
- 24 29. Gordon T, Kannel WB, Castelli WP, Dawber TR. Lipoproteins, cardiovascular disease,
- 25 and death. The Framingham study. *Arch Intern Med* 1981;**141**(9): 1128-31.
- 26 30. Shimamoto T, Iso H, Iida M, Komachi Y. Epidemiology of cerebrovascular disease:
- 27 stroke epidemic in Japan. *J Epidemiol* 1996;**6**(3 Suppl): S43-7.
- 28 31. Evenson KR, Rosamond WD, Cai J, et al. Physical activity and ischemic stroke risk.
- 29 The atherosclerosis risk in communities study. *Stroke* 1999;**30**(7): 1333-9.
- 30 32. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of
- 31 coronary heart disease. *Am J Epidemiol* 1990;**132**(4): 612-28.
- 32 33. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients
- 33 with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from
- 34 the American Heart Association/American Stroke Association Council on Stroke: co-
- 35 sponsored by the Council on Cardiovascular Radiology and Intervention: the American
- 36 Academy of Neurology affirms the value of this guideline. *Stroke* 2006 ;**37**(2): 577-617.
- 37 34. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and
- 38 coronary heart disease. *Psychosomatic medicine* 2005 May-Jun;**67** Suppl 1: S29-33.
- 39 35. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression
- 40 and heart disease. *Neuroscience and biobehavioral reviews* 2002;**26**(8): 941-62.
- 41 36. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and
- 42 inflammatory risk markers for coronary heart disease. *The American journal of cardiology*
- 43 2002;**90**(12): 1279-83.
- 44 37. Stewart JC, Janicki DL, Muldoon MF, Sutton-Tyrrell K, Kamarck TW. Negative
- 45 emotions and 3-year progression of subclinical atherosclerosis. *Archives of general psychiatry*
- 46 2007;**64**(2): 225-33.
- 47 38. Lichtman JH, Bigger JT, Jr., Blumenthal JA, et al. Depression and coronary heart
- 48 disease: recommendations for screening, referral, and treatment: a science advisory from the
- 49 American Heart Association Prevention Committee of the Council on Cardiovascular Nursing,
- 50 Council on Clinical Cardiology, Council on Epidemiology and Prevention, and
- 51 Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the
- 52 American Psychiatric Association. *Circulation* 2008;**118**(17): 1768-75.
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

**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 $\geq$ 10)*	Antidepressant filled (%)**
<b>All</b>	23282 (100)	203 (0.90)	129 (0.60)	4562 (19.6)	927 (4.0)
<b>Sex</b>					
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)
<b>Age-group (years)</b>					
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)
<b>Education</b>					
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)
<b>Current smoker</b>					
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)
<b>High alcohol intake (<math>\geq</math>200 g/week)</b>					
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)
<b>Obesity (BMI<math>\geq</math>30)</b>					
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)
<b>Sedentary life style (&lt;2 MET hours/day)</b>					
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)
<b>Hypertension or diabetes</b>					
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  $\geq$  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)
<b>Model 1</b>				
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)***	130/23946	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)
<b>Model 2</b>				
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)***	130/23946	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)
<b>Model 3</b>				
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)***	130/23946	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)
<b>Model 4</b>				
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)***	130/23946	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&lt;0.05, \*\* p&lt;0.01, \*\*\* p&lt;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