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Does depression predict coronary heart disease and cerebrovascular disease equally well? The Health and Social Support Prospective Cohort Study

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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) with 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 23 282 adults (9507 men, 13 775 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 $\geqslant 10$ on the 21-item Beck Depression Inventory, and 2.04 (1.27–3.27) for those who filled antidepressant prescriptions compared with 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

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 evidece 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]

Although 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[1] 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 European Prospective Investigation of Cancer (EPIC)-Norfolk study[17] also showed that major depressive disorders are not associated with incident stroke in a large sample of participants aged 41–80 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.

Methods

Population

The 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 $\geqslant 10$[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 outpatient 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 were 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 CHD and CBVD

The personal identification number of participants was used to collect records of hospitalizations 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 1 January 1999 and 31 December 2005. Disease endpoint, based on the main diagnoses, was determined

by International Classification of Disease (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 $\geqslant$ 30 vs $<$30 kg/m^2). Physical activity was calculated using the metabolic equivalent task (MET) index to measure sedentary life style [$<$2 MET-hours (MET-h) per day] (No vs Yes).

Statistical analysis

Differences in CHD, CBVD and depression (defined as BDI score $\geqslant$10 or filling antidepressant prescriptions) as a function of sample characteristics were assessed using the chi-square test. We examined the relationships between depression and cardiovascular outcomes (CHD and CBVD events) using four serially adjusted Cox regression models. In model 1, depression and sex, age and education were the sole independent variables. In model 2 and 3, the hazard ratios (HRs) were adjusted for behavioural (alcohol consumption, sedentary lifestyle and smoking) and biological (obesity, hypertension or diabetes and incident CHD or CBVD) risk factors, respectively. In model 4, the HRs were simultaneously adjusted for all aforementioned covariates. In addition to these analyses, we examined the association between continuous BDI scores to determine the risk of CHD and CBVD associated with a 1-unit increase in BDI. There is no evidence of interactions between depression and sex in relation to CHD and CBVD status ($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 23 282 participants with complete data on covariates were included in the analyses. A total of 203 incident CHD events (fatal or non-fatal ischaemic 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 non-traumatic intracranial haemorrhage, 19 other CBVDs, 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 ($P \leqslant 0.026$). Depression among participants at baseline (BDI score $\geqslant$10 or filling antidepressant prescriptions) was more likely among women, older people, those with a lower education, current smokers, high alcohol consumers, obese people, those more likely to have a sedentary life style and those with hypertension or diabetes ($P \leqslant 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 socio-demographic variables, the HR for CHD was 1.66 [95% confidence interval (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 with 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 socio-demographic 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.

Table 1 Number of incident CHD, CBVD and depression as a function of covariates

Baseline covariates	Participants (%)	CHD (%)	CBVD (%)	Depression (%) (BDI ⩾ 10)	Antidepressant filled (%)[a]
All	23 282 (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	13 775 (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	15 547 (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	21 017 (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	21 050 (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-h/day)					
No	17 903 (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	22 201 (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 $P \leqslant 0.026$, except for the association between smoking and CBVD.
[a]Participants who filled prescriptions for antidepressant drugs identified from the National Prescription Register.
CBVD = cerebrovascular disease.

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 were 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 2 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 at 2.08 ($P < 0.001$) and 2.15 ($P < 0.006$) when compared with 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

Table 2 Depression as a predictor of CHD and CBVD

Depression	CHD		CBVD	
	No. of events/no. of participants	HR (95% CI)	No. of events/no. of participants	HR (95% CI)
Model 1				
Not depressed (BDI ⩽ 9)	138/18 720	1.00	100/18 720	1.00
Depressed (BDI ⩾ 10)	65/4562	1.66 (1.24–2.24)***	29/4562	1.01 (0.67–1.53)
BDI score (continuous)	203/23 282	1.04 (1.02–1.06)***	129/23 282	1.01 (0.99–1.04)
Filled antidepressant prescriptions	19/927	2.04 (1.27–3.27)**	11/927	1.77 (0.95–3.29)
Model 2				
Not depressed (BDI ⩽ 9)	138/18 720	1.00	100/18 720	1.00
Depressed (BDI ⩾ 10)	65/4562	1.51 (1.11–2.03)**	29/4562	0.92 (0.61–1.40)
BDI score (continuous)	203/23 282	1.04 (1.02–1.06)***	129/23 282	1.01 (0.98–1.04)
Filled antidepressant prescriptions	19/927	1.86 (1.15–2.99)**	11/927	1.61 (0.86–3.00)
Model 3				
Not depressed (BDI ⩽ 9)	138/18 720	1.00	100/18 720	1.00
Depressed (BDI ⩾ 10)	65/4562	1.62 (1.20–2.18)***	29/4562	0.93 (0.60–1.42)
BDI score (continuous)	203/23 282	1.04 (1.02–1.06)***	129/23 282	0.98 (0.96–1.01)
Filled antidepressant prescriptions	19/927	1.89 (1.18–3.05)**	11/927	1.61 (0.86–3.00)
Model 4				
Not depressed (BDI ⩽ 9)	138/18 720	1.00	100/18 720	1.00
Depressed (BDI ⩾ 10)	65/4562	1.47 (1.08–1.99)**	29/4562	0.87 (0.57–1.32)
BDI score (continuous)	203/23 282	1.03 (1.02–1.05)***	129/23 282	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: 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 CHD or incident CBVD.
Model 4: HR adjusted for all aforementioned variables.

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 with 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 depression 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 ($P = 0.097$) and 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 CHD with that for 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 (BDI 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 socio-demographics and bio-behavioural risk factors, only the associations between depression and incident CHD remained evident. A similar pattern

of associations was 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 Centre for Epidemiological Studies Depression Scale (CES-D), the study showed that in older post-menopausal women without a history of CHD or CBVD, depressive symptoms were not associated with an increased risk of incident stroke: unadjusted and adjusted HRs 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 events 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, are 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[26] 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 BDI. 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,[27–29] we conducted *post hoc* analyses stratifying the sample by hypertension and diabetes status. In participants without hypertension and diabetes, sex–age–education adjusted HRs for CHD were 1.43 ($P = 0.046$) for those with mild to severe depressive symptoms, i.e. scoring $\geqslant 10$ on the 21-item BDI, and 1.79 ($P = 0.052$) for those who filled antidepressant prescriptions compared with 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 HRs for CHD were 2.27 ($P = 0.006$) for those with mild to severe depressive symptoms, i.e. scoring $\geqslant 10$ on the 21-item BDI, and 2.43 ($P = 0.031$) for those who filled antidepressant prescriptions compared with 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 categorized into a dichotomous variable using the standard cut-off, and CBVD, even in analysis adjusted simply for socio-demographic 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 (six out of nine 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 41–80 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 with 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.[30] 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, whereas its influence on ischaemic heart disease is less clear, particularly in the male population.[31] Furthermore, several prospective studies have reported either a U-shaped or no association between physical activity and stroke,[32] whereas current evidence clearly indicates its protective influence on CHD risk.[33] Finally, recent guidelines for prevention of stroke suggest that the effect of alcohol and obesity on stroke is complex and controversial, which 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 equally.

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 that 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),[35] hypothalamic–pituitary–adrenal axis dysregulation (increased cortisol secretion),[36] enhanced inflammatory processes (higher levels of interleukin-6, C-reactive protein and fibrinogen)[37] and accelerated progression of atherosclerosis as indicated by change in carotid intima-media thickness.[38] Depression could also be linked to CHD via behaviour-related factors.[39] 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 subclinical 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 bio-behavioural 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. First, 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, CBVD endpoint-based on the main diagnosis was defined using ICD-10 codes I60–I69 (i.e. stroke and other CBVDs), 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 CBVD subtypes, such as ischaemic and haemorrhagic 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 antidepressant 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 2 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 severely 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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KEY MESSAGES

- The relationship between depression and CBVD continues to be debated although little research has compared the predictive power of depression for CHD with that for CBVD within the same population.
- After adjustment for basic socio-demographic factors and bio-behavioural risk factors, participants with mild to severe depressive symptoms, i.e. those scoring $\geqslant 10$ on the 21-item BDI, and those who filled antidepressant prescriptions had an increased risk for CHD over the 7 years of follow-up compared with those without depression markers.
- There was no clear evidence that depression is a risk factor for CBVD, but this needs further confirmation.

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