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Research report

Cardiovascular disease in persons with depressive and anxiety disorders

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ABSTRACT

Background: Associations between depression, and possibly anxiety, with cardiovascular disease have been established in the general population and among heart patients. This study examined whether cardiovascular disease was more prevalent among a large cohort of depressed and/or anxious persons. In addition, the role of specific clinical characteristics of depressive and anxiety disorders in the association with cardiovascular disease was explored.

Methods: Baseline data from the Netherlands Study of Depression and Anxiety were used, including persons with a current (i.e. past year) or remitted DSM-IV depressive or anxiety disorder ($N = 2315$) and healthy controls ($N = 492$). Additional clinical characteristics (subtype, duration, severity, and psychoactive medication) were assessed. Cardiovascular disease (stroke and coronary heart disease) was assessed using algorithms based on self-report and medication use.

Results: Persons with current anxiety disorders showed an about three-fold increased prevalence of coronary heart disease (OR anxiety only = 2.70, 95%CI = 1.31–5.56; OR comorbid anxiety/depression = 3.54, 95%CI = 1.79–6.98). No associations were found for persons with depressive disorders only or remitted disorders, nor for stroke. Severity of depressive and anxiety symptoms—but no other clinical characteristics—most strongly indicated increased prevalence of coronary heart disease.

Limitations: Cross-sectional design.

Conclusions: Within this large psychopathology-based cohort study, prevalence of coronary heart disease was especially increased among persons with anxiety disorders. Increased prevalence of coronary heart disease among depressed persons was largely owing to comorbid anxiety. Anxiety—alone as well as comorbid to depressive disorders—as risk indicator of coronary heart disease deserves more attention in both research and clinical practice.

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1. Introduction

In 1993 Frasure-Smith et al. showed that after a myocardial infarction, depressed persons were four-to-five times as likely to die within the next six months than their non-depressed

counterparts. Although this initial observation turned out to overestimate the true relationship between depression and heart disease (e.g. Nicholson et al., 2006), since then, many studies have examined their association. Both depression and heart disease are leading disorders when considering disease burden. The World Health Organization projected depression and heart disease to become numbers 1 and 2, respectively, on the list of diseases with the greatest loss of 'disability adjusted life years' in 2030 in high-income countries and numbers 2 and 3 worldwide (Mathers and Loncar, 2006). This suggests an

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enormous possible gain in public health and disease burden when depression, heart disease and especially their comorbidity could be prevented through increasing knowledge on the link between these two disabling diseases.

Research thus far has mainly focused on two kinds of populations: heart disease patients and the general population. Meta-analyses have shown that among heart patients depression is associated with an 1.8 to 2.6 increased risk of a subsequent cardiovascular event or death (Barth et al., 2004; Nicholson et al., 2006; van Melle et al., 2004), while in the general population depression increases risk of cardiovascular disease (CVD) about 1.6 to 1.8 times (Nicholson et al., 2006; Rugulies, 2002; Van der Kooy et al., 2007; Wulsin and Singal, 2003). Although, as suggested by Nicholson et al. (2006), these estimates may still be inflated due to incomplete and biased reporting of adjustment for conventional risk factors and CVD severity. Studies on prevalence of CVD within a psychopathology-based population are largely lacking. From a psychiatrist perspective, it would be of great importance to know whether clinically depressed patients indeed have a higher prevalence of CVD and how much increased exactly this prevalence is. What's more, it has hardly been addressed whether specific characteristics of depression, such as age of onset, duration, or severity of the disorder could further determine the exact CVD probability, or whether the association is restricted to specific subtypes, such as atypical or melancholic depression. This knowledge could give insight into underlying mechanisms that relate depression and CVD as well as into which patients should be most closely monitored for cardiovascular dysfunctioning.

Besides depression, some studies have suggested anxiety to be associated with CVD as well (Albert et al., 2005; Fan et al., 2008; Kawachi et al., 1994). Anxiety disorders lead to comparable levels of disability as depression and heart disease (Buist-Bouwman et al., 2006) and have been found to increase risk of premature all-cause and cardiovascular death (Denollet et al., 2009; Phillips et al., 2009). The association between anxiety and CVD, however, has been far less studied than the link between depression and heart disease. Even less studied has been the association between anxiety characteristics (subtype, duration, and severity) and CVD. Furthermore, as depression and anxiety are often found to be comorbid, it would be of great importance to study the association between depression and anxiety with CVD in concert. This could shed light on the specificity of associations between depressive and anxiety disorders and CVD.

Therefore, in the present study within a large cohort of depressed and/or anxious persons and healthy controls we examined the (extent of the) association between the presence of a psychiatric diagnosis of depressive and/or anxiety disorder with CVD. In addition, we assessed the specificity of these associations by directly comparing depressive with anxiety disorders and by examining whether specific characteristics of depressive and/or anxiety disorders (subtype, duration, severity, and psychoactive medication) could be identified that indicate increased probability of CVD.

2. Methods

2.1. Sample

The Netherlands Study of Depression and Anxiety (NESDA) is an ongoing cohort study designed to investigate the long-

term course and consequences of depressive and anxiety disorders. Participants were 18 to 65 years old at baseline assessment in 2004–2007 and were recruited from the community (19%), general practice (54%) and secondary mental health care (27%). A total of 2981 persons were included, consisting of persons with a current or past depressive and/or anxiety disorder ($N=2329$) and healthy controls ($N=652$). A detailed description of the NESDA study design and sampling procedures can be found elsewhere (Penninx et al., 2008). The research protocol was approved by the Ethical Committee of participating universities and after complete description of the study all respondents provided written informed consent.

As subclinical symptoms of on the one hand depressive and anxiety disorders and on the other hand CVD could to a certain degree resemble each other (e.g. feeling tired or pain on the chest) and could therefore falsely indicate or elevate an association between them, persons with subthreshold symptoms of depression or anxiety but no formal diagnosis of depressive or anxiety disorder ($N=158$) and persons who self-reported CVD without reporting accompanying appropriate medication use ($N=16$) were excluded (see below for more details), leaving 2807 persons for the present analyses.

2.2. Psychopathology and clinical characteristics

Presence of depressive disorder (major depressive disorder and dysthymia) and anxiety disorder (social phobia, generalized anxiety disorder, panic disorder and agoraphobia) was established using the Composite Interview Diagnostic Instrument (CIDI) according to DSM-IV criteria (American Psychiatric Association, 2001). The CIDI is a highly reliable and valid instrument for assessing depressive and anxiety disorders (Wittchen, 1994) and was administered by specially trained research staff. Based on CIDI, participants were categorized as having no, current (i.e. in past year), or a remitted (lifetime, but not current) depressive and/or anxiety disorder. In addition, a categorical variable was constructed classifying persons as having no depressive or anxiety disorder, remitted depressive or anxiety disorder, current depressive disorder only, current anxiety disorder only, or current depressive and anxiety disorder.

Clinical characteristics examined included the subtype, duration and severity of the depressive or anxiety disorder. Next to CIDI diagnoses, subtypes of depressive disorder included first onset versus recurrent major depressive disorder (based on CIDI interview), presence of an atypical symptom profile, and presence of a melancholic symptom profile. Atypical symptom profile (mood reactivity and ≥ 2 of hyperphagia, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity) was constructed by comparison of items of the 28-item self-report Inventory of Depressive Symptoms (IDS (Rush et al., 1996)) with DSM-IV criteria for atypical depression following Novick's algorithm (Novick et al., 2005). Similarly, melancholic symptom profile (lack of mood reactivity or loss of pleasure and ≥ 3 of distinct mood quality, mood worse in morning, early morning awakening, psychomotor retardation or agitation, anorexia/weight loss, and guilt feelings) was constructed based on comparison of IDS items with DSM-IV criteria using the algorithm proposed by Khan (Khan et al., 2006). Additionally, for both depressive

and anxiety disorders a distinction was made between late onset (≥ 30 years old) and early onset (< 30 years old) of the psychiatric disorder, as derived from the CIDI interview. Using the Life Chart method (Lyketsos et al., 1994), a detailed account of the presence of depressive and anxiety symptoms during the past four to five years was assessed among persons with depressive or anxiety disorders. From this, the percent of time patients reported depressive or anxiety symptoms was computed as a measure of duration. Severity of depressive symptoms was assessed by means of the IDS; severity of anxiety symptoms by means of the 21-item Beck Anxiety Inventory (BAI (Beck et al., 1988)).

To account for possible psychoactive medication effects, medication use was assessed based on drug container inspection of all drugs used in the past month and classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification (WHO Collaborating Centre for Drug Statistics Methodology, 2007). As effects of psychoactive medication are likely negligible when used infrequently, use of psychoactive medication was only considered present when taken on a regular basis (at least 50% of the time). Antidepressants included selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (N06AA) and other antidepressants (N06AF/N06AX). Benzodiazepines included ATC-codes N03AE, N05BA, N05CD and N05CF.

2.3. Cardiovascular disease

Cardiovascular disease (CVD) included stroke, angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty and coronary artery bypass grafting and was adjudicated using standardized algorithms considering self-report and medication use (based on drug container inspection and ATC coding). During the interview, participants were asked if they ever had a stroke, a heart condition or a heart attack, and to specify the kind of condition. In addition, it was asked whether subjects were ever troubled by chest pain during physical strain and whether the pain disappeared within 10 min after standing still or taking a tablet under the tongue. If subjects responded positively on both questions this was regarded as an indication of angina pectoris (symptoms). Stroke was identified by self-report supported by use of either anticoagulant/antiplatelet agents (antithrombotic agents [ATC-code B01], acetylsalicylic acid [N02BA01; $\geq 50\%$ use of ≤ 100 mg], or carbasalate calcium [N02BA15]), any medication for hypertension (antihypertensives [C02], diuretics [C03], beta blocking agents [C07], calcium channel blockers [C08], agents acting on renin-angiotensin system [C09]), or lipid modifying agents (C10). Angina pectoris and myocardial infarction were only considered present when self-report (or symptoms) of the disease was supported by use of medication for coronary heart disease (CHD; beta blocking agents [C07], nitrate vasodilators [C01DA], calcium channel blockers [C08], or anticoagulant/antiplatelet agents [B01, N02BA01 $\geq 50\%$ use of ≤ 100 mg, N02BA15]). When self-report was not confirmed by medication use, CVD was considered to be 'undetermined' and subjects were excluded from the analyses ($N=16$). When angina symptoms ($N=510$) were not supported by medication use, persons were considered as having no CVD ($N=413$). Percutaneous transluminal coronary angioplasty

and coronary artery bypass grafting were based on self-report only. CVD was subdivided into stroke and CHD (angina pectoris, myocardial infarction, angioplasty or bypass). For sensitivity analyses, as beta blockers are sometimes prescribed for anxiety symptoms, a secondary measure of CHD excluded persons with symptoms of angina pectoris and use of a beta blocker only (N excluded = 32).

2.4. Covariates

Sociodemographic characteristics included age, sex, and years of education. As lifestyle characteristics can be associated with both CVD and depression/anxiety, smoking status (never, former, current), alcohol intake (< 1 , 1–14, > 14 drinks per week), physical activity (measured with the International Physical Activity Questionnaire (Craig et al., 2003) in MET-minutes [ratio of energy expenditure during activity compared to rest times the number of minutes performing the activity] per week) and body mass index (BMI; weight in kilograms divided by height in meters squared) were assessed.

2.5. Statistical analyses

Sample characteristics were compared across persons with and without CVD using independent t -tests for continuous variables and chi-square statistics for dichotomous and categorical variables. Logistic regression analyses assessed the association with CVD for depressive and anxiety disorders separately and simultaneously, before and after adjustment for a priori selected covariates (sociodemographic [age, sex, years of education] and lifestyle [smoking status, alcohol intake, physical activity, BMI]). Next, consistency of associations with regard to CVD were assessed by conducting separate adjusted logistic regression analyses for subtypes of CVD (stroke and CHD) and subtypes of CHD (angina pectoris, myocardial infarction, and CHD surgery [angioplasty or bypass]).

Specificity of associations with regard to clinical aspects of the depressive or anxiety disorder was assessed in a subsample of persons with current depressive and/or anxiety disorders using sociodemographic-adjusted logistic regression analyses. First, the association with CVD of depressive disorder versus anxiety disorder was directly compared. Second, associations between specific depressive disorder or anxiety disorder characteristics (subtype, duration, severity, and psychoactive medication use) and CVD were examined.

3. Results

Mean age of the present sample was 41.8 (SD = 13.0) years, 66.4% were women, 19.4% had a remitted and 63.1% had a current depressive or anxiety disorder, while 5.6% had CVD. Table 1 describes sample characteristics comparing persons with and without CVD. Persons with CVD were older, more often men, less educated, more often former smoker, less often moderate drinker, and had a higher BMI. Also, persons with CVD more often had a current anxiety disorder, but not depressive disorder.

Table 2 describes the results of unadjusted and adjusted logistic regression analyses assessing the association of depressive and anxiety disorders with CVD. Remitted disorders were

Table 1
Sample characteristics by cardiovascular disease status.

	No CVD N = 2651	CVD N = 156	<i>p</i> ^a
Sociodemographic variables			
Age, years, mean (SD)	41.1 (12.9)	54.1 (7.8)	<.001
Women, %	67.7	45.5	<.001
Years of education, mean (SD)	12.2 (3.3)	11.0 (3.2)	<.001
Lifestyle variables			
Smoking status			
Never, %	28.4	18.6	.001
Former, %	32.3	46.2	
Current, %	39.3	35.3	
Alcohol intake			
<1 drink a week, %	32.2	37.8	.05
1–14 drinks a week, %	52.1	42.3	
>14 drinks a week, %	15.7	19.9	
Physical activity (in MET-minutes/week), mean (SD)	3720 (3046)	3423 (3198)	.24
Body mass index, mean (SD)	25.4 (5.0)	28.6 (4.8)	<.001
Depression and anxiety variables			
Depressive disorder			
No depressive disorder, %	30.6	23.7	.14
Remitted depressive disorder, %	24.4	29.5	
Current (in past year) depressive disorder, %	45.0	46.8	
Anxiety disorder			
No anxiety disorder, %	37.9	26.3	.007
Remitted anxiety disorder, %	14.6	14.1	
Current (in past year) anxiety disorder, %	47.5	59.6	
Depressive and/or anxiety disorder			
No depressive or anxiety disorder	17.8	12.2	.03
Remitted depressive or anxiety disorder	19.4	19.2	
Current depressive disorder only	15.2	9.0	
Current anxiety disorder only	17.7	21.8	
Current depressive and anxiety disorder	29.8	37.8	

^a Based on independent *t*-test for continuous variables and chi-square statistics for dichotomous and categorical variables.

not statistically significantly associated with CVD, but after adjustment current depressive and current anxiety disorders were (OR = 1.59, 95%CI = 1.02–2.47; OR = 2.18, 95%CI = 1.45–3.28, respectively). When the presence or absence of a depressive or anxiety disorder was combined in one categorical

variable, odds of CVD were increased for persons with a current anxiety disorder alone (OR = 1.96, 95%CI = 1.06–3.64) as well as for those with a combined current anxiety and depressive disorder (OR = 2.35, 95%CI = 1.33–4.20) compared to healthy controls. Increased likelihood of CVD was not observed for persons with a current depressive disorder only (OR = 0.93, 95%CI = 0.44–1.96).

Next, effects of depression/anxiety status were assessed separately for odds of having stroke and odds of having CHD (Table 3). Depressive and anxiety disorders were not associated with stroke. In contrast, persons with a current anxiety disorder were 2.5 to 3.5 times more likely to have CHD (OR anxiety only = 2.70, 95%CI = 1.31–5.56; OR anxiety and depression = 3.54, 95%CI = 1.79–6.98). No significant association was found for persons with a depressive disorder only (OR = 1.41, 95%CI = 0.61–3.23). To gain some insight into the direction of the association between psychopathology and CHD, we repeated the current analysis among persons with an early onset (≤ 30 years) of depressive or anxiety disorder (*N* excluded = 269). Since CHD hardly occurs before the age of 30, an early onset suggests that psychopathology was present before CHD. Within persons with an early onset of depressive or anxiety disorder similar results were found (OR depression only = 1.37, 95%CI = 0.59–3.20; OR anxiety only = 2.37, 95%CI = 1.12–5.03; OR anxiety and depression = 3.26, 95%CI = 1.59–6.68; data not tabulated). An additional analysis excluded persons (*N* = 32) who ‘earned’ their status of CHD only based on angina symptoms and use of a beta blocker—sometime used to relieve anxiety symptoms—, but substantial associations remained (OR anxiety only = 2.06, 95%CI = 0.96–4.44; OR anxiety and depression = 2.89, 95%CI = 1.41–5.93; data not tabulated). When examining CHD subtypes (angina pectoris, myocardial infarction, and CHD surgery) associations for current anxiety disorder (with or without depressive disorder) were found for all (see Table 3). Depressive disorders alone also showed increased odds of especially angina pectoris and myocardial infarction, but these were not statistically significant. Because associations of psychopathology were only found with CHD and not stroke, all following analyses were conducted with CHD as the outcome.

Fig. 1 shows that within persons with current psychopathology (*N* = 1770), persons with a current anxiety disorder

Table 2
Association^a of depressive and anxiety disorders with cardiovascular disease.

	<i>N</i>	Unadjusted			Adjusted		
		OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Depressive disorder							
No depressive disorder	847		REF			REF	
Remitted depressive disorder	693	1.56	1.00–2.43	.05	1.50	0.93–2.40	.10
Current (in past year) depressive disorder	1267	1.34	0.89–2.01	.16	1.59	1.02–2.47	.04
Anxiety disorder							
No anxiety disorder	1046		REF			REF	
Remitted anxiety disorder	408	1.40	0.82–2.38	.22	1.31	0.74–2.30	.35
Current (in past year) anxiety disorder	1353	1.81	1.24–2.64	.002	2.18	1.45–3.28	<.001
Depressive and/or anxiety disorder							
No depressive or anxiety disorder	492		REF			REF	
Remitted depressive or anxiety disorder	544	1.45	0.81–2.62	.21	1.27	0.68–2.37	.45
Current depressive disorder only	418	0.86	0.43–1.74	.68	0.93	0.44–1.96	.85
Current anxiety disorder only	504	1.80	1.01–3.20	.05	1.96	1.06–3.64	.03
Current depressive and anxiety disorder	849	1.86	1.10–3.16	.02	2.35	1.33–4.20	.004

^a Based on logistic regression analyses unadjusted and adjusted for age, sex, years of education, smoking status, alcohol use, physical activity and BMI.

Table 3
Association^a of depressive and anxiety disorders with cardiovascular disease subtypes.

	Cardiovascular disease subtypes (N = 156)						Coronary heart disease subtypes (N = 138)								
	Stroke (N = 36)			Coronary heart disease (N = 133)			Angina pectoris (N = 105)			Myocardial infarction (N = 50)			CHD surgery (N = 48)		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
No depressive or anxiety disorder	REF			REF			REF			REF			REF		
Remitted depressive or anxiety disorder	0.73	0.24–2.19	.57	1.65	0.79–3.43	.18	2.17	0.88–5.34	.09	2.55	0.78–8.40	.12	1.44	0.49–4.24	.50
Current depressive disorder only	0.53	0.13–2.18	.38	1.41	0.61–3.23	.42	2.16	0.82–5.71	.12	2.58	0.70–9.46	.15	1.60	0.50–5.10	.42
Current anxiety disorder only	1.02	0.34–3.11	.97	2.70	1.31–5.56	.007	2.87	1.16–7.11	.02	3.47	1.03–11.66	.05	2.69	0.94–7.67	.06
Current depressive and anxiety disorder	1.37	0.49–3.86	.55	3.54	1.79–6.98	<.001	4.96	2.14–11.49	<.001	4.75	1.46–15.47	.01	2.24	0.79–6.37	.13

^a Based on logistic regression analyses adjusted for age, sex, years of education, smoking status, alcohol use, physical activity and BMI; in all analyses the specific CVD or CHD subtype was compared to persons without any CVD (N = 2651).

had almost 80% increased odds to have CHD compared to persons with a current depressive disorder (OR = 1.77, 95% CI = 0.89–3.54), albeit this was not statistically significant. Odds of CHD for persons having an anxiety disorder in addition to a depressive disorder were more than twofold increased compared to having a depressive disorder alone (OR = 2.40, 95%CI = 1.27–4.54).

Table 4 shows the results of separate sociodemographic-adjusted logistic regression analyses examining associations of depressive and anxiety disorder characteristics with CHD in the sub-sample of persons with current psychopathology (N = 1770). No specific subtype of depressive disorder was associated with CHD. For persons with a current anxiety disorder associations with CHD were consistent for persons with generalized anxiety disorder, social phobia, panic disorder and agoraphobia. Duration of depressive or anxious complaints was also not associated with CHD. However, the severity of depressive symptoms (OR per SD increase = 1.32, 95%CI = 1.05–1.65) and of anxiety symptoms (OR per SD increase = 1.36, 95%CI = 1.11–1.66) were significantly associated with CHD. In fact, it appeared that the results from Fig. 1 showing a somewhat higher OR in persons with comorbid depression and anxiety in comparison to the OR in persons with anxiety disorders alone could be explained by

severity of symptoms. After additional adjustment for severity of depressive and anxiety symptoms, odds of CHD for persons with anxiety disorders were equally increased, irrespective of additional depressive disorder (OR anxiety only = 1.86, 95%CI = 0.91–3.79; OR anxiety and depression = 1.95, 95%CI = 1.00–3.78). Lastly, psychoactive medication use did not statistically significantly increase odds of CHD, but a trend was found for use of benzodiazepines and higher odds of CHD (OR = 1.60, 95%CI = 0.95–2.71). Benzodiazepine use did not affect the before presented results (i.e. ORs of CHD as presented in Table 3 and Fig. 1 were very similar after additional adjustment for benzodiazepine use).

4. Discussion

This study examined the association between diagnosed depressive and anxiety disorders and cardiovascular disease within a large cohort of depressed and/or anxious persons and healthy controls. The results show that, individually, both depressive and anxiety disorders are associated with CVD. However, the increased prevalence of CHD among depressive persons appeared to be mainly owing to comorbidity of anxiety disorders. No associations were found with stroke. Severity of depressive and anxiety symptoms—but no other clinical factors—identified those with the highest prevalence of CHD.

Relatively few studies have examined the link between anxiety and CHD and most of these studies assessed anxiety symptoms, but not diagnosis. Although the link between anxiety (symptoms) and CHD has been more consistently found in initially CHD-free populations than among heart patients (Suls and Bunde, 2005), a recent study (Frasure-Smith and Lesperance, 2008) showed that both a generalized anxiety disorder, as well as severity of anxiety symptoms were associated with an increased risk of major adverse cardiac events in patients with stable coronary artery disease. Our results demonstrate that within a psychopathology-based population the prevalence of CHD is increased across a wide range of diagnosed anxiety disorders (social phobia, generalized anxiety disorder, panic disorder and agoraphobia). In fact, persons who suffered from any anxiety disorder in the past year were about three times as likely to have CHD. Given the widespread prevalence of anxiety disorders, these results suggest that the role of anxiety disorders in CHD is important

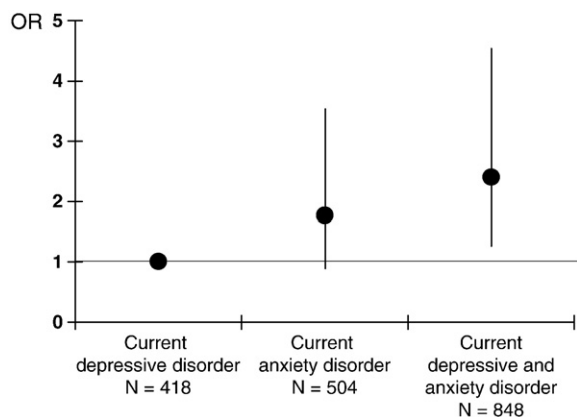


Fig. 1. OR (based on logistic regression analyses adjusted for age, sex, and education) for CHD in persons with a current depressive and/or anxiety disorder.

Table 4

Association of depressive and anxiety disorder characteristics with coronary heart disease.

	No CHD <i>N</i> = 1673		CHD <i>N</i> = 97		<i>p</i>
	% or mean (SD)		% or mean (SD)		
	Unadjusted		Adjusted ^a		
Type of depressive disorder ^b					
First onset major depressive disorder (vs. recurrent)	46.4	41.8	0.95	0.56–1.61	.85
Atypical symptoms	20.8	24.2	1.53	0.83–2.83	.17
Melancholic symptoms	11.9	16.7	1.08	0.53–2.18	.84
Late onset (≥30 years old)	35.0	61.8	1.11	0.65–1.92	.70
Type of anxiety disorder ^c					
Generalized anxiety disorder	44.9	50.0	1.15	0.72–1.82	.56
Social phobia	55.5	53.6	1.08	0.68–1.72	.74
Panic disorder	55.1	53.6	1.13	0.71–1.80	.62
Agoraphobia	16.0	25.0	1.21	0.70–2.10	.49
Late onset (≥30 years old)	22.6	43.4	1.06	0.65–1.73	.83
Duration ^d					
Percent of time with symptoms in past 4 years	52.4 (35.6)	58.8 (35.3)	1.02	0.56–1.86	.95
Severity ^d					
Current depressive symptoms score (IDS)	28.5 (12.4)	32.2 (13.0)	1.32 ^e	1.05–1.65	.02
Current anxiety symptoms score (BAI)	16.5 (10.8)	20.0 (9.7)	1.36 ^e	1.11–1.66	.003
Psychoactive medication ^d					
Selective serotonin reuptake inhibitor use	25.1	21.6	0.87	0.52–1.45	.60
Tricyclic antidepressant use	3.8	7.2	1.56	0.68–3.57	.30
Other antidepressant use	8.8	12.4	1.26	0.65–2.41	.49
Benzodiazepine use	10.5	22.7	1.60	0.95–2.71	.08

^a Based on logistic regression analyses adjusted for age, sex, and education; each line represents a single analysis.^b Within sub-sample of persons with a current (past year) depressive disorder: *N* = 1266; first onset vs. recurrent: persons with dysthymia only (*N* = 44) were excluded.^c Within sub-sample of persons with a current (past year) anxiety disorder: *N* = 1352.^d Within sub-sample of persons with a current (past year) depressive and/or anxiety disorder: *N* = 1770.^e Per SD increase: IDS: SD = 12.9; BAI: SD = 10.7.

and has been largely overlooked thus far. These findings also suggest that cardiac symptoms in anxiety persons might really indicate heart disease and underdiagnosing heart disease in anxiety patients might be a problem.

The possible overlap in symptoms between anxiety disorders and heart disease could also pose a problem in examining the association between these two. We tried to handle this issue by only including definite cases of anxiety and by confirmation of medication use appropriate for CVD. Even when further excluding persons with symptoms of chest pain and use of a beta-blocker only—sometimes described to relieve anxiety symptoms—associations of anxiety disorders with CHD remained. Moreover, associations between anxiety disorders and CHD were found across different types of both CHD and anxiety disorders and were not confined to for instance angina pectoris and panic disorder, supporting the conclusion that the strong association observed between anxiety and CHD is real.

Although a depressive disorder diagnosis was associated with CVD, this relationship appeared to be largely explained by comorbid anxiety. Previous research in the general population and among heart patients consistently showed an association between depression and CVD. Importantly, these studies often did not take into account comorbid anxiety, but many depressed persons have a comorbid anxiety disorder (in our sample 67%). Similar to our study within a psychopathology-based population, Strik et al. (2003) found that anxiety and not depressive symptoms were an independent predictor of cardiac events among heart

patients and accounted for the relationship between depressive symptoms and cardiac events. Longitudinal studies should further disentangle the associations between depression, anxiety and CHD.

Considering clinical characteristics, highest prevalences of CHD were found among those with the most severe symptoms of depression and anxiety. This might suggest that more severe symptoms induce an extra increased risk of CHD. Otherwise, as symptom scales of depression and anxiety often include a set of somatic items, it is possible that severity of depression or anxiety partly reflects severity of heart complaints (Sorensen et al., 2005). Otherwise, somatic health factors might be more important in depressive disorders that are associated with CVD. This might also (partly) explain why other studies, mostly conducted within somewhat older populations, which generally have more somatic conditions, do find more support of a relationship between depression and CVD.

Little evidence was found of other clinical characteristics of depressive or anxiety disorders to be specifically related to CHD. Although we had expected longer lasting psychiatric disorders to be associated with higher prevalence of CVD, the results did not corroborate this. This finding somewhat decreases the plausibility of depressive and anxiety disorders directly causing CVD. Also, associations with remitted psychiatric disorders were not statistically significant, perhaps partly due to decreased reliability of diagnosis assessment in the more far away past. On a more positive side, this might suggest that when persons remit from depressive or anxiety disorders, the

odds of CHD decreases. Further, antidepressant medication use was not associated with CHD. Tricyclic antidepressants have been well described to have cardiovascular effects (Glassman, 1998), but this might have been counterbalanced in our study by the fact that these medications are therefore contraindicated in heart patients. Benzodiazepine use was somewhat more prevalent among persons with CHD, but whether they increase risk of CVD or whether this finding is a reflection of poorer health status in persons with CVD, cannot be decided from this study.

Interestingly, our results only show an association with CHD, but not with stroke. Although some studies do relate psychopathology to stroke (Everson et al., 1998), this has been much less examined than CHD. We examined the association between depression, anxiety and stroke in a relatively young population where stroke was not very prevalent and we were not able to distinguish between ischemic or a hemorrhagic stroke. As an association of depression and anxiety with specifically ischemic stroke is expected, hemorrhagic strokes might have diluted the association.

Our study has some important strengths. We made use of a large sample of persons with diagnosed psychopathology to investigate whether true psychiatric diagnoses of both depression and anxiety are indeed associated with a heightened prevalence of CVD. Furthermore, we were able to examine the effects of a large amount of clinical characteristics of depressive and anxiety disorders. Some limitations have to be noted as well. Our results are based on cross-sectional data. This makes it impossible to draw any conclusions about the causality of associations between depressive and anxiety disorders and CHD. However, a strong association between anxiety disorder and CHD existed in persons with an onset of psychopathology before 30 years. Since CHD hardly occurs before the age of 30, an early onset suggests that psychopathology was present before CHD. Additionally, as depression and anxiety are highly comorbid and had an early onset in most persons (only 269 of 2315 had late onset), it is unlikely that the finding that anxiety is more strongly than depression associated with CHD was biased by the cross-sectional design. Another limitation is that the presence of heart disease was not verified by general practice or hospitalization records. However, self-report was confirmed by medication use and previous research has shown good concordance between self-report of heart disease and general practitioners information, with especially little over-reporting (Kehoe et al., 1994; Kriegsman et al., 1996).

In conclusion, our results show that anxiety disorders are more strongly associated with coronary heart disease than depressive disorders and might partly account for the widely reported association between depression and heart disease. The highest prevalence of CHD is found among those with the most severe psychiatric symptoms, such as those persons with comorbid depression and anxiety. Anxiety as possible risk factor for cardiovascular disease needs to be more elaborately investigated in future research, and deserves more attention in clinical care as well.

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Study sponsors had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

All other authors declare that they have no conflicts of interest.

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