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Depression, anxiety and 6-year risk of cardiovascular disease

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ABSTRACT

Objective: Depression and anxiety are considered etiological factors in cardiovascular disease (CVD), though their relative contribution and differentiation by clinical characteristics have not been studied intensively. We examined 6-year associations between depressive and anxiety disorders, clinical characteristics and newly-developed CVD.

Methods: DSM-IV diagnoses were established in 2510 CVD-free participants of the Netherlands Study of Depression and Anxiety. Data on subtype, severity, and psychoactive medication were collected. The 6-year incidence of CVD was assessed using Cox regression analyses adjusted for sociodemographic, health and lifestyle factors.

Results: One-hundred-six subjects (4.2%) developed CVD. Having both current depressive and anxiety disorders (HR = 2.86, 95%CI 1.49–5.49) or current depression only (HR = 2.30; 95%CI 1.10–4.80) was significantly associated with increased CVD incidence, whereas current anxiety only (HR = 1.48; 95%CI 0.74–2.96) and remitted disorders (HR = 1.48; 95%CI 0.80–2.75) were not associated. Symptom severity was associated with increased CVD onset (e.g., Inventory of Depressive Symptomatology per SD increase: HR = 1.51; 95%CI 1.25–1.83). Benzodiazepine use was associated with additional CVD risk (HR = 1.95; 95%CI 1.16–3.31).

Conclusions: Current depressive (but not anxiety) disorder independently contributed to CVD in our sample of initially CVD-free participants. CVD incidence over 6 years of follow-up was particularly increased in subjects with more symptoms, and in those using benzodiazepines.

Introduction

According to the World Health Organisation, ischemic heart disease and cerebrovascular disease have been and will be leading causes of death for decades [1]. Longitudinal research thus far has provided us with potential etiological factors of cardiovascular disease (CVD), including those concerning negative mental health. Meta-analytic studies have demonstrated that anxiety [2] and depression [3] increase the incidence of CVD in healthy populations by 26% to 81%. Despite the high co-morbidity between these psychiatric disorders [4,5], most previous studies examined the influence of either depression or anxiety on CVD, or examined both but showed the effect size for one condition. The relative contribution of depressive and anxiety disorders to the development of CVD therefore remains unclear. In addition, many studies have assessed depression or anxiety symptoms by using self-report measures, which are more likely to overdiagnose psychopathology and thereby artificially inflate the effect size of an association with CVD in the presence of underlying somatic health problems. Particular clinical characteristics may also elucidate the association between depression, anxiety and CVD. For clinical practice it is of great importance to know whether specific subgroups of depressed or anxious patients carry a higher CVD risk and should be closely monitored for cardiovascular dysfunction. Despite the heterogeneity in depression and anxiety, the potentially differentiating role of disorder subtype in the association with CVD has only sparsely received attention. With respect to symptom severity, some prospective studies support a dose–response association between severity of depressive or anxiety symptoms and CVD [6–9]. As to the use of psychoactive medication and subsequent CVD, some studies found a detrimental cardiovascular effect for tricyclic antidepressants (TCAs) [10–13], serotonin reuptake inhibitors (SSRIs) or other antidepressants [12], and benzodiazepines [14], whereas others found no significant association (TCAs [15]; SSRIs/other antidepressants [10,11]; benzodiazepines [13,15]).

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Aims of the study

Our aim was to examine the specificity of associations between depressive and anxiety disorders and development of CVD over 6 years of follow-up. In addition, we aimed to investigate the role of clinical characteristics (subtype, severity, use of psychoactive medication) in these associations. Analyses were based on data from a population of initially CVD-free subjects with depressive and/or anxiety disorders and healthy controls.

Material and methods

Sample

The Netherlands Study of Depression and Anxiety (NESDA) is an ongoing longitudinal cohort study to examine the course of depressive and anxiety disorders. In order to represent various health care settings and stages of psychopathology, participants were recruited from community, primary care and outpatient psychiatric clinics. The community sample builds on two cohorts: the Netherlands Mental Health Survey and Incidence Study (NEMESIS) [16], a cohort based on a random sample of private households in 90 Dutch municipalities; and the Adolescents at Risk for Anxiety and Depression study (ARIADNE) [17], a cohort of biological children of parents who were treated for depressive or anxiety disorder. Primary care respondents were recruited from 65 general practitioners in the vicinity of the field sites (Amsterdam, Groningen, Leiden). From a random sample of patients who consulted their GP in the last four months for any reason, both screen positives and screen negatives were invited to participate. Specialized mental health patients were recruited from outpatient clinics for mental health care around the three research sites. Newly enrolled patients who received a primary diagnosis of depressive or anxiety disorder were asked to participate. Exclusion criteria were not being fluent in Dutch and having a primary diagnosis of a psychiatric disorder not subject of NESDA which will largely affect course trajectory: psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder. The NESDA sample included 2329 subjects with a current or remitted depressive and/or anxiety disorder, and 652 controls, aged 18 through 65 years at the baseline assessment (2004–2007). The research protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent. Further details of the NESDA rationale, recruitment strategy and methods have been described elsewhere [18]. For the present investigation, we used data from NESDA baseline, 2-year, 4-year and 6-year examinations.

For the current study, participants with baseline data only ($n = 276$) and those with CVD at baseline ($n = 153$) were excluded. Subjects who had an 'undetermined' CVD status after 6 years of follow-up ($n = 11$; see below for more details) were also excluded, leaving 2541 subjects for the present analyses. As compared with included participants, excluded subjects ($n = 471$) were older (45.9 versus 41.2 years, $p < .001$), more often male (40.9% versus 32.3%, $p < .001$), less educated (11.2 versus 12.3 years, $p < .001$), and more often suffering from a depressive or anxiety disorder (1-month diagnosis 60.9% versus 45.0%, $p < .001$).

Depression and anxiety

During the NESDA baseline examination, the presence of depressive disorders (major depression [single or recurrent], dysthymia) and anxiety disorders (social phobia, panic disorder with or without agoraphobia, agoraphobia without panic, generalized anxiety disorder) was established using the DSM-IV based [19] Composite International Diagnostic Interview (CIDI; WHO version 2.1). The CIDI is a highly reliable and valid instrument for assessing psychopathology [20] and was administered by trained research staff. Participants were consequently categorized as having no, remitted (lifetime, but not current) or current (i.e. in past month) depressive and/or anxiety disorder. A categorical variable was constructed classifying subjects 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 (i.e. current comorbidity).

Severity of symptoms was measured with the 30-item self-report version of the Inventory of Depressive Symptomatology ($IDS\text{-}SR_{30}$) [21], the 21-item Beck Anxiety Inventory (BAI) [22], the 15-item Fear Questionnaire (FQ; measures avoidance) [23], and the 16-item Penn State Worry Questionnaire (PSWQ) [24]. Factor analyses in previous research [25,26] showed a two-factor solution, in which factor 1 (Worry Engagement) has demonstrated higher internal consistency and significantly stronger correlations with measures of depression and anxiety compared with the total PSWQ score and factor 2 (Absence of Worry). We therefore use the sum of 11 positively scored items.

Psychoactive medication use was assessed based on drug container inspection of all drugs used in the past month. Medication was classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification [27]. Use of antidepressant medication (TCAs, N06AA; SSRIs, N06AB; other antidepressants [serotonin and norepinephrine reuptake inhibitors; SNRIs], N06AX) or benzodiazepines (ATC-codes N03AE, N05BA, N05CD and N05CF) was considered present when taken at least 50% of days for the past month, which applied to 98.4% of antidepressant users and 47.3% of benzodiazepine users.

Cardiovascular disease

Cardiovascular disease included stroke and coronary heart disease (CHD; angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty or 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, heart attack, or heart condition, and to specify the kind of condition. When self-report was not confirmed by medication use, CVD was considered to be 'undetermined' and subjects ($n = 11$) were excluded from the analyses. Since chest pain can be a symptom of either angina or panic disorder, subjects reporting this symptom without using appropriate medication were considered to have no CVD. Percutaneous transluminal coronary angioplasty and coronary artery bypass grafting were based on self-report only. See Table 1 for the self-report responses and mentioned medications leading to a report of incident CVD.

Covariates

Socio-demographic characteristics included age, sex and years of education. Health related variables included hypertension and diabetes mellitus. The presence of hypertension was based on the use of any antihypertensive medication (ATC codes C02, C03, C07, C08, C09). The presence of diabetes was based on fasting glucose levels ≥ 7 mmol/l (blood drawn in the morning, analyzed using standard laboratory techniques) or the use of blood-glucose lowering medication (ATC code A10). Fasting triglyceride levels (mmol/l) were based on standard laboratory techniques and adjusted for the use of triglyceride-lowering medication (C10AB, C10AD, C10BA01). Furthermore, several lifestyle factors were taken into account. Body mass index (BMI) was calculated and smoking status was defined as non-smoker, former smoker or current smoker. Alcohol intake was measured as the amount of alcoholic consumptions a week. Physical activity was assessed with the Physical Activity Questionnaire [28] in MET-minutes [ratio of energy expenditure during physical activity times the number of minutes performing the activity] per week.