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Associations between life stress and subclinical cardiovascular disease are partly mediated by depressive and anxiety symptoms

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ABSTRACT

Background: Stress experienced during childhood or adulthood has been associated with cardiovascular disease (CVD), but it is not clear whether associations are already prevalent on a subclinical cardiovascular level. This study investigates associations between indicators of life stress and subclinical CVD, and whether these are mediated by depression and anxiety.
Methods: Subjects were 650 participants of the Netherlands Study of Depression and Anxiety, aged 20–66 years, with or without (27.5%) depressive and anxiety disorders. Life stress included childhood trauma, negative life events and recently experienced daily hassles or job strain. Subclinical CVD was measured as 1) carotid atherosclerosis (intima–media thickness and the presence of plaques) using B-mode ultrasonography, and 2) central arterial stiffness (heart rate normalized augmentation index) using calibrated radial applanation tonometry.
Results: Increased central arterial stiffness was shown in subjects who had experienced childhood trauma (per SD increase: $\beta = .07$; $p = .01$), or reported recently experienced daily hassles (per SD increase: $\beta = .06$; $p = .02$), negative life events (per SD increase: $\beta = .05$; $p = .03$), or job strain (high versus low: $\beta = .09$; $p = .01$). Associations between life stress and arterial stiffness appeared to be partly mediated by severity of depressive and anxiety symptoms. No significant associations were found for childhood life events, nor between indicators of life stress and carotid atherosclerosis.
Conclusions: Childhood trauma and recent life stress were associated with increased central arterial stiffness. This suggests that life stress – partly via depression and anxiety – might enhance the development and progression of CVD.

Introduction

Atherosclerosis and arterial stiffening are among the primary processes leading to cardiovascular disease (CVD) [1–3]. The development of these abnormalities already starts during childhood [4–6]. Many risk factors are known to be associated with the development of CVD, such as smoking and sedentary lifestyle. Stressful circumstances during childhood and adulthood may also play a role, although their precise contribution is unknown.

Previous studies have shown that childhood adversities (e.g., abuse, neglect, life events and household dysfunction) are associated with CVD in adulthood [7–12]. Childhood adversities were associated with self-reported ischemic heart disease in members of a health appraisal center [7,8]. Another study has found that coronary heart disease (CHD) patients more often reported severe illness of a family member and

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; NESDA, Netherlands Study of Depression and Anxiety disorders; LDL, low density lipoprotein; CIMT, carotid intima–media thickness; CIMTbif, bifurcation carotid intima–media thickness; AIx, augmentation index; AIx75, central augmentation index normalized for a heart rate of 75 beats per minute; MAP, mean arterial pressure; ATC, Anatomical Therapeutic Chemical; BMI, body mass index; MET, metabolic equivalent; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; CIDI, Composite International Diagnostic Interview; IDS, Inventory of Depressive Symptomatology; BAI, Beck Anxiety Inventory

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serious conflicts during their childhood as compared with controls [9]. Others found longitudinal evidence that subjects who had experienced adversities or traumas during childhood had increased risk of subsequent CVD [10,11]. Furthermore, evidence was found that women who experienced severe physical or sexual abuse as a child had higher risks of cardiovascular events in early adulthood; both retrospective and prospective cases were included [12].

Stressful circumstances during adulthood have also been associated with increased CVD risk [13,14]. Acute stressors can lead to sudden cardiac death [15] and feelings of tension and frustration have shown to induce myocardial infarction [16]. Furthermore, perceived mental stress [17] and posttraumatic stress disorder [18] are associated with risk of CHD. With respect to adulthood stress, job stress (i.e., strain: high demand, low control) in particular has been thoroughly investigated [19–26]. Chronic job strain after myocardial infarction is associated with increased risk of recurrent cardiovascular events [19]. Demanding work has been associated with the development of subclinical CVD, measured as carotid atherosclerosis [22] or arterial stiffness [23] in working-populations. However, the evidence is contradictory, since other studies found no associations in women while they did in man [21,24] and even negative associations in healthy male employees [20,25] between job stress and carotid atherosclerosis or arterial stiffness. Recently, a meta-analysis of published and unpublished data in over 197,000 participants has shown that job strain is associated with a small, but consistent, increased risk of CHD [26].

To date, most studies have focused on clinical CVD in association with a particular source of life stress (either during childhood or recent) [7–19]. Apart from a remarkable amount of data regarding the link between job stress and carotid atherosclerosis [20–22,25], arterial stiffness [23,24], or CHD [26], the associations between other sources of life stress and subclinical vascular health in one population have not been studied yet. Furthermore, childhood stress [10,27,28], and recent stress [29,30] have been associated with depression and anxiety, and in turn, these conditions have been associated with cardiovascular morbidity and mortality [31–33].

Aims of the study

In light of the above, the aims of this study are 1) to investigate the associations between (childhood and recent) life stress and indicators of subclinical cardiovascular disease, i.e., carotid atherosclerosis and central arterial stiffness and 2) to determine whether these associations are independent of or mediated by depression and anxiety.

Methods

Sample

The present study was conducted as an extension of the 2-year assessment of the Netherlands Study of Depression and Anxiety (NESDA), 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 NESDA baseline sample (2004–2007) included 2329 persons with a lifetime depressive and/or anxiety disorder, and 652 controls, aged 18 through 65 years and of predominantly North European origin. Details of the study rationale, recruitment strategy and methods have been described elsewhere [34]. The research protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent.

Of the 2981 baseline participants invited, 2596 participated in the 2-year assessment. Predictors of non-response included younger age, lower education and major depressive disorder at baseline [35]. After the 2-year assessment, participants were asked for permission to be approached for additional cardiovascular measurements. Six hundred and fifty participants (response rate 66.9%) who lived in the area close to the location of measurements underwent additional cardiovascular measurements, see flow chart in Fig. 1. Median time between the NESDA 2-year assessment and cardiovascular assessment (carotid ultrasound and arterial stiffness measurements) was 68 days.

Of the eligible subjects, non-participants were younger (mean: 43.9 versus 46.5 years, $p = .001$), more likely to be female (71.8% versus 64.7%, $p = .03$) and more often had lifetime depressive and/or anxiety disorder (81.9% versus 72.7%, $p = .001$), as compared with participants. Participants and non-participants did not differ with respect to a history of CVD, smoking status, blood pressure and use of lipid-modifying or antihypertensive medication.

Life stress measures

Childhood stress

At the NESDA baseline assessment, a Dutch semi-structured interview was conducted in order to gather information on childhood life events and trauma, as was done previously [36]. Participants were asked if any of the following *negative life events* had happened before the age of 16 years: death of biological father or mother, divorce of parents, placement in care (children's home/juvenile prison/foster family). Since only 29 participants had experienced more than one life event, a dichotomous index was constructed.

Participants were also asked whether or not they had experienced any kind of *trauma* before the age of 16 years. Emotional neglect included lack of parental attention and support, or ignoring of one's problems and experiences. Psychological abuse was defined as verbal abuse, undeserved punishment, subordination to siblings and blackmailing. Physical abuse included being kicked, hit, beaten up, or otherwise. Sexual abuse was defined as being sexually approached against one's will, i.e., being touched or forced to touch someone in a sexual way. Participants were then asked whether the reported trauma had occurred once, sometimes, regularly, often or very often. Answers were categorized into 0 = absent,

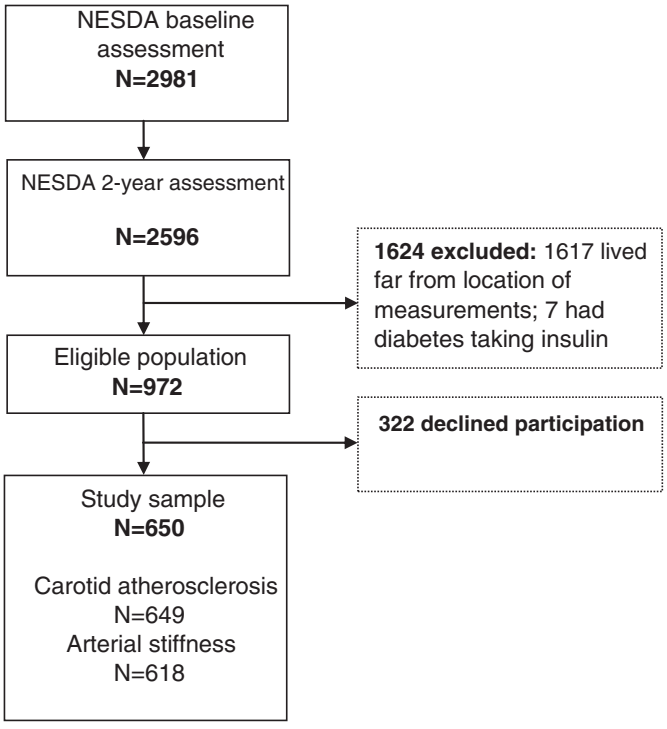

Fig. 1. Flow chart of study population. NESDA = Netherlands Study of Depression and Anxiety.