Psychoneuroendocrinology (2012) 37, 48—55

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journal homepage: www.elsevier.com/locate/psyneuen

Psychological distress, cortisol stress response and subclinical coronary calcification

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Received 22 December 2010; received in revised form 4 May 2011; accepted 4 May 2011

KEYWORDS
Mental health;
Psychological distress;
Cortisol reactivity;
Stress responses;
Coronary artery calcification

Summary
Objectives: Poor mental health has been associated with coronary heart disease (CHD). One hypothesized underlying mechanism is hypothalamus pituitary adrenal axis dysfunction. We examined the associations between psychological distress, cortisol response to laboratory-induced mental stress and subclinical coronary artery calcification (CAC).
Participants: 527 volunteers free of CHD (mean age = 63.0 ± 5.7 years), drawn from the Whitehall II cohort.
Measures: CAC was measured using electron beam computed tomography. Current distress at time of the heart scan was indicated by a Short Form-36 mental health score, whereas long-term distress was based on the averaged scores of six assessments over the 15 preceding years. Salivary cortisol was measured in response to mental stressors (Stroop, mirror tracing).
Results: Detectable CAC was found in 56.4% (mild/moderate: 46.9%; severe: 9.5%) of the sample. After adjustment for sociodemographics and conventional risk factors, long-term but not current psychological distress was associated with a higher risk of severe CAC (OR per SD increase = 1.49, 95%CI = 1.03—2.16). Psychological distress was not significantly associated with cortisol stress response. A trend for interaction (p = .09) indicated that individuals with long-term poor mental health and high cortisol reactivity showed the highest odds for severe CAC.
Conclusions: Long-term but not current psychological distress is associated with severe CAC in healthy older subjects. Although psychological distress generally was not associated with cortisol stress responses, participants with both long-term distress and increased cortisol response were especially at risk for severe calcification.

1. Introduction

Poor mental health has been frequently associated with heightened cardiovascular risk, because depressive symptoms or disorders increase the risk of coronary heart disease

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0306-4530
doi:10.1016/j.psyneuen.2011.05.001

(CHD), and vice versa (Nicholson et al., 2006). The development of vascular imaging techniques has made it possible to assess subclinical atherosclerosis, which can help delineate the temporal relationship between mental health and CHD. However, findings are conflicting, possibly due to heterogeneity in design and measures used. A positive association between current poor mental health and carotid or coronary atherosclerosis has been found in some (Tiemeier et al., 2004; Faramawi et al., 2007), but not in other studies (O'Malley et al., 2000; Diez Roux et al., 2006). Long-term poor mental health as indicated by either recurrent depressive episodes or repeatedly measured depressive symptoms has been associated with carotid plaque (Jones et al., 2003) and coronary or aortic calcification (Agatisa et al., 2005; Hamer et al., 2010a), but not with carotid intima-media thickness (IMT) (Rice et al., 2009). Long-term as compared to current psychological distress can be expected to have a stronger association with subclinical atherosclerosis, because it may indicate a higher and more chronic stress exposure.

Various etiological pathways have been suggested that link depression to accelerated atherogenesis, ultimately resulting in CHD. In addition to an unhealthy lifestyle (Bonnet et al., 2005), biological pathways may be involved, including dysregulation of the hypothalamic pituitary adrenal (HPA) axis (Grippo and Johnson, 2002). Increased diurnal cortisol exposure (indicated by higher overall levels (Dekker et al., 2008) or smaller decline (Matthews et al., 2006)), which suggest a higher HPA axis activation in reaction to stress, has been associated with subclinical atherosclerosis. Concerning depression and HPA-axis functioning, divergent observations have been done in proof of associations between depression and hypo- or hypercortisolemia (Oldehinkel et al., 2001; Otte et al., 2004; Bremmer et al., 2007; Vreeburg et al., 2009). One study has shown that 'hypercortisolemic depressed' people were at increased risk of metabolic syndrome — a clustering of cardiovascular risk factors (Vogelzangs et al., 2007). Another important way to examine the contribution of hypothesized etiological pathways is through acute psychophysiological stress testing (Dimsdale, 2008). Longitudinal follow-up studies have shown that individuals with large mental-stress induced cardiovascular responses are more likely to have a poor future cardiovascular health status (Chida and Steptoe, 2010). Literature on the relationship between laboratory-induced cortisol stress responses and subclinical atherosclerosis is sparse, revealing only one study that showed an association between cortisol reactivity and coronary artery calcification (CAC) (Hamer et al., 2010b). In contrast, a study among patients with manifest coronary disease has demonstrated that patients exhibit blunted HPA-axis reactivity as compared with healthy controls (Nijm et al., 2007). Regarding cortisol stress responses in major depressive disorder, a meta-analysis has reported that depressed patients generally have impaired cortisol response recovery but also blunted cortisol reactivity (mostly in afternoon studies) (Burke et al., 2005). It is still unclear to what extent HPA axis responsiveness can provide an etiological explanation for the association between poor mental health and subclinical atherosclerosis.

Most studies have examined cross-sectional associations between mental health and subclinical disease. The present study is one of the first to assess both concurrent and long-term measures of psychological distress in relation to subclinical atherosclerosis, and to explore HPA axis reactivity as a linking mechanism. Data were analyzed from older participants without a prior history of CHD. We hypothesized those participants with long-term psychological distress poor mental health would have higher risk of CAC, and that this association would be attributable to a greater cortisol stress reactivity, or be particularly present in individuals with 'hypercortisolemic distress'.

2. Methods

2.1. Participants

Participants were a subgroup of the Whitehall II epidemiological cohort, recruited into the Heart Scan Study. Whitehall II is an ongoing study examining demographic, psychosocial and biological risk factors for coronary heart disease (Marmot et al., 1991). The criteria for entry into the Heart Scan (2006—2008) included no history or objective signs of CHD, no previous diagnosis or treatment for hypertension, diabetes, inflammatory diseases, or allergies. Participants with a history of major depression (self-report of diagnosis by a physician) or using antidepressant medication in the 12 months prior to the psychophysiological testing were also excluded. From the Whitehall II participants (n = 1169) initially invited, 27.6% were not eligible (mainly because of prescribed medications) and 25.9% declined to take part. The total Heart Scan sample included 543 participants of white European origin, aged 53—76 years. All participants gave full informed consent to participate in the study and ethical approval was obtained from the University College London committee on the Ethics of Human Research. Sixteen individuals had missing data on the main factors of analyses, leaving a final sample of 527. Fig. 1 shows the design of the main predictors and outcome variables.

2.2. Psychological distress measurement

Self-reported psychological distress was assessed using the Mental Health Index (MHI-5), a 5-item subscale of the Short Form-36 health survey (Ware and Sherbourne, 1992; McHorney et al., 1993). Though developed to measure well-being in general populations, the MHI-5 also has proven well in detecting major depression (AUC = 0.89) and anxiety disorders (AUC = 0.74) (Berwick et al., 1991) and has shown a Spearman correlation of r = 0.79 with the Beck Depression Inventory (Rogers et al., 2005). Besides, it has been associated with future CHD (Whang et al., 2009). The MHI-5 consists of five 6-level Likert items asking about the amount of time the individual had felt nervous, down in dumps/blue, calm/peaceful, downhearted/low, and happy during the past month. The sum of ratings is transformed to a score ranging 0—100. Because higher scores indicate more psychological well-being, we transformed the scores so that high scores indicated high distress. The MHI-5 was assessed at five time points before the Heart Scan Study (1991/1993, 1995/1997, 1997/1999, 2001, 2003/2004) as well as during the study itself (2006/2008). In case of one (n = 69) or two (n = 8) missing scores, imputation with the average score over available data was performed. Because major depression was an