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The impact of stress systems and lifestyle on dyslipidemia and obesity in anxiety and depression

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Summary
Background: Dyslipidemia and obesity have been observed in persons with severe anxiety or depression, and in tricyclic antidepressant (TCA) users. This likely contributes to the higher risk of cardiovascular disease (CVD) in anxiety and depressive disorders. We aimed to elucidate whether biological stress systems or lifestyle factors underlie these associations. If so, they may be useful targets for CVD prevention and intervention.
Methods: Within 2850 Netherlands Study of Depression and Anxiety (NESDA) participants, we evaluated the explaining impact of biological stress systems (i.e., the hypothalamic—pituitary—adrenal [HPA] axis, autonomic nervous system [ANS] and inflammation) and lifestyle factors (i.e., tobacco and alcohol use, and physical activity) on adverse associations of anxiety and depression severity and TCA use with high and low-density lipoprotein cholesterol, triglycerides, body mass index and waist circumference. Through linear regression analyses, percentual change (%Δ) in β was determined and considered significant when $\%\Delta > 10$.
Results: The inflammatory marker C-reactive protein had the most consistent impact (explaining 14—53% of the associations of anxiety and depression severity and TCA use with lipid and obesity levels), followed by tobacco use (explaining 34—43% of the associations with lipids). The ANS mediated all associations with TCA use (explaining 32—61%). The HPA axis measures did not explain any of the associations.

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Conclusions: Increased dyslipidemia and (abdominal) obesity risk in patients with more severe anxiety disorders and depression may be partly explained by chronic low-grade inflammation and smoking. TCAs may increase metabolic risk through enhanced sympathetic and decreased parasympathetic ANS activity. That the HPA axis had no impact in our sample may reflect the possibility that the HPA axis only plays a role in acute stress situations rather than under basal conditions.

1. Introduction

The classical cardiovascular disease (CVD) risk factors dyslipidemia (i.e., high total, low-density lipoprotein [LDL] cholesterol or triglycerides, or low high-density lipoprotein [HDL] cholesterol) and (abdominal) obesity are found to be more common in patients with anxiety disorders and depression (Gil et al., 2006; Skilton et al., 2007; Vogelzangs et al., 2007; Dunbar et al., 2008; Koponen et al., 2008; Vaccarino et al., 2008; Miettola et al., 2008; Pizzi et al., 2008; Akbaraly et al., 2009). Previously, we demonstrated that not all anxious or depressed patients display higher dyslipidemia and obesity risk. Dyslipidemia and obesity appeared to be particularly present in those with more severe anxiety or depression symptomatology (van Reedt Dortland et al., 2010b), and in users of tricyclic antidepressants (TCAs) (van Reedt Dortland et al., 2010a). Dyslipidemia and obesity were not related to the use of selective serotonin re-uptake inhibitors (SSRIs) or other antidepressants. The associations of dyslipidemia and obesity with more severe symptoms of depression and anxiety and with TCA use likely contribute to the generally increased prevalence of CVD (Kubzansky et al., 2006; Whooley et al., 2008) and diabetes mellitus (Engum, 2007) in persons with depressive and anxiety disorders. In order to create anchor points in prevention and treatment of CVD and diabetes, it is of importance to understand the underlying mechanisms.

Several underlying mechanisms may be involved. Hypothalamic–pituitary–adrenal (HPA) axis dysregulation (Holsboer, 2000; Vreeburg et al., 2009a, 2010) as well as decreased parasympathetic and increased sympathetic autonomic nervous system (ANS) activity (Licht et al., 2008, 2010a; Pizzi et al., 2008) and elevated inflammatory markers such as C-reactive protein (CRP), interleukin(IL)-6 (Pizzi et al., 2008; Bankier et al., 2009; Howren et al., 2009) and tumor necrosis factor-alpha (TNF-α) (Penninx et al., 2003) have been detected in anxiety and depression and among TCA users (Barden et al., 1995; Licht et al., 2008) Also, unfavorable lifestyle habits such as increased tobacco and alcohol consumption and decreased physical activity (Rodgers et al., 2000; Bonnet et al., 2005; O'Donnell et al., 2006; Bots et al., 2008; Sanchez-Villegas et al., 2009; Skogen et al., 2009) have been observed in patients with mood disorders. In turn, these HPA axis (Bjorntorp and Rosmond, 2000; Anagnostis et al., 2009; Veen et al., 2009), ANS (Tsujii and Bray, 1998), inflammatory (Esteve et al., 2005) and lifestyle (Craig et al., 1989; Latour et al., 1999; NCEP, 2002) alterations are thought to induce dyslipidemia and (abdominal) obesity. Those mechanisms could therefore lie in the causal pathway, ultimately increasing CVD risk in people with anxiety and depressive disorders. If so, they may be useful targets for prevention and intervention.

Within the Netherlands Study of Depression and Anxiety (NESDA) we aim to identify the mechanisms that underlie the relationship of anxiety and depressive severity and TCA use with dyslipidemia and obesity, with possible candidates being biological stress system (i.e., HPA axis, ANS and inflammation) perturbations or lifestyle (i.e., tobacco or alcohol use and physical activity). We are the first to evaluate the role of those potential mechanisms in concert, in a large cohort study.

2. Methods and materials

2.1. Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), an 8-year longitudinal cohort study including 2981 persons aged 18–65 years. Subjects were recruited from community, primary care, and mental health care in the Netherlands. Persons with depressive and anxiety disorders as well as healthy controls were included. For the current study, only cross-sectional baseline data were available. The baseline assessment comprised a face-to-face interview, written questionnaires and biological measurements. The study design has been described in detail elsewhere (Penninx et al., 2008). The study protocol was approved by the Ethical Review Board of each participating center, and all subjects signed informed consent at the baseline assessment.

For the current analyses, we excluded 40 (1.3%) subjects with missing values on anxiety or depression severity or on TCA use (see below), and 91 (3.1%) subjects with missing values on lipid or obesity measures (see below), which resulted in a sample of 2850 (95.6%) subjects. In analyses on TCA use, subjects who used TCAs (n = 78) were compared with subjects who did not use any antidepressant at all (n = 2138), whereas all other analyses were conducted in the entire group (n = 2850).

2.2. Measurements

2.2.1. Anxiety and depression severity and TCA use

Anxiety severity was assessed by the 21-item self report Beck Anxiety Inventory (BAI) ranging from 0 to 63 (Beck et al., 1988). Depression severity was assessed by the 30-item Inventory of Depressive Symptoms self report (IDS-SR) ranging from 0 to 84 (IDS guide, 2008). TCA use (Anatomical Therapeutic Chemical [ATC] (WHO, 2008) code N06AA) within the past month was registered by observation of drug containers brought in.

2.2.2. Lipid and obesity measures

HDL and LDL cholesterol, triglycerides, body mass index (BMI) and waist circumference (WC) were previously found to be